CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-228 S006

MEDICAL REVIEW

NDA 21-228 – SE-8 supplement 006

BPCA Clinical Review

Drug: Detrol LA Capsules (tolterodine tartrate)

1.0 Brief Background:

Detrol LA is currently approved in adults for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. NDA 21-228 (supplement 006) contains pediatric efficacy and safety studies including pharmacokinetic data and proposed labeling in response to a written request for pediatric studies to be performed in both neurologically impaired and neurologically normal children. The submission contains no new CMC or pharmacology/toxicology information. The Pediatric Exclusivity Board met on January 5, 2004, and granted an additional 6-month exclusivity for both NDA 21-228 (Detrol LA) and NDA 20-771 (Detrol).

2.0 Executive Summary and Recommendation:

Based on the clinical and pharmacokinetic data submitted in response to a Pediatric Written Request, this supplement may be **approved**. Efficacy was not demonstrated in either the neurologically impaired or neurologically normal pediatric patient populations. New safety information from the pediatric studies should be incorporated into the Detrol LA label.

3.0 Overview of Submitted Efficacy and Safety Studies:

In response to the written request, the sponsor submitted the results of 3 studies in neurologically impaired children (001, 002, and 003), 2 studies in neurologically intact children with symptoms of urgency incontinence (008 and 020), and an open-label extension safety study (021) containing subjects from Studies 020 and 018. In addition, 2 pharmacokinetic (PK) studies (018 and 044) and two bioequivalence studies (004 and 005) were submitted.

Studies in neurologically impaired children:

Study #	N	age	formulation	dose	placebo
001	19	1 mo-4yrs	syrup	0.03, 0.60, 0.12 mg/kg/day	no
002	15	5-10 yrs	syrup	0.03, 0.60, 0.12 mg/kg/day	no
003	11	11-15 yrs	Detrol LA	2, 4, 6 mg/day	no

Studies in neurologically intact children:

Study #	N	Age	Formulation	Dose	Placebo
008	369	5-10 yrs	Detrol LA	2 mg/day	Yes Drug:plac = 2:1
020	342	5-10 yrs	Detrol LA	2 mg/day	Yes Drug:plac = 2:1

4.0 Studies in neurologically impaired children

The trial designs of the 3 studies (001, 002, and 003) in neurologically impaired patients were nearly identical except for the ages of the patients and the formulations studied.

Studies 001 and 002 were 12 week, multicenter, open-label, dose escalation, PK, pharmacodynamic (PD), clinical efficacy and safety studies. Patients were enrolled within 3 months of a baseline urodynamic evaluation. In 001 and 002, dosing was initiated at 0.03 mg/kg/day in two divided doses and maintained for four weeks. Following review of the safety data, the dose was escalated to 0.06 mg/kg/day for four weeks and then to 0.12 mg/kg/day for four weeks. Urodynamic data, patient diary data, and safety data were collected at the end of each dose period. PK data were collected only at the 0.06 mg/kg/day dose. The drug formulation used in Trials 001 and 002 was an investigational product, tolterodine tartrate oral solution (1 mg/5 cc) which is not commercially available. The mid-range dose (0.06 mg/kg/day) was chosen to approximate the exposure of adults receiving 2 mg bid of the tolterodine IR tablet. In study 003 (10 to 15 year-old group), all patients received Detrol LA 2 mg for 4 weeks, then 4 mg for 4 weeks, and finally 6 mg for 4 weeks. Patients enrolled in Trial 003 who were unable to swallow the capsule(s) were allowed to empty the capsule and consume the beads sprinkled over food.

Inclusion criteria included patients with stable neurological disease (meningomyelocoele, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia. Patients were required to need intermittent catheterization for management of urinary drainage. Exclusion criteria included use of an indwelling cathether within 4 weeks of enrollment, clinically significant urinary tract infection, and treatment with a potent CYP 3A4 inhibitor within 7 days of any study measurements.

Endpoints included both data obtained from urodynamic evaluation and data derived from patient diaries. Urodynamic endpoints were: 1) volume to first detrusor contraction of > 10 cm H_20 pressure 2) functional bladder capacity and leak point pressure 3) intravesical volume at 20 and 30 cm H_20 pressure 4) maximal cystometric capacity (intravesical volume at 40 cm H_20 pressure) 5) bladder compliance and 6) percent change in cystometric capacity. Diary derived endpoints were: 1) mean number of catheterizations or micturitions per 24 hours 2) mean volume per catheterization/micturition and 3) mean number of incontinence episodes/24 hours. Diary data were based on means derived from three-day diary recordings done at baseline and at each dose period (weeks 4, 8, and 12).

4.1 Trial 001 (Drug formulation is syrup):

Nineteen patients (10 boys and 9 girls) were enrolled. More than 80% were Caucasian. Three patients were less than 6 months of age, 6 were between 6 months and 2 years, and 10 were between 2 and 4 years of age. Eighteen patients had myelomeningocele and one had experienced a spinal cord injury.

Changes from baseline in urodynamic measurements are shown in Table 1.

Table 1. Study 001 Change from baseline urodynamic variables

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)	42.6 (21.1)	50.9 (30.8)	71.3 (43.6)	2.1 (1.1)	1.7 (1.0)	1.8 (1.1)
	N	19	19	19	19	13	12	19	13	12
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)	2.4 (28.6)	-3.2 26.4)	-10 (36.0)	0.1 (1.4)	-0.1 (0.9)	-0.3 (0.9)
	N	17	19	18	18	12	9	18	12	9
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	15.9 (30.5)	**31.7 (54.7)**	-8.4 (14.4)	**37.1 (52.2)**	24.1 (45.7)	46.0 (74.0)	**1.9 (2.6)**	0.8 (1.5)	1.2 (1.8)
	N	16	18	16	14	8	6	14	8	7
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**34.4 (61.4)**	32.5 (63.7)	-3 (14.3)	**29.2 (46.9)**	27.2 (59.5)	12.8 (40.1)	**1.5 (2.3)**	0.9 (2.0)	0.3 (1.0)
	N	17	17	14	15	9	5	15	9	5

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary data (Trial 001) are shown in Table 2.

Table 2. Study 001 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	4.8 (1.4)	5.2 (1.9)	34.9 (16.1)
	N	18	18	18
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	-0.1 (1.1)	-0.2 (2.0)	5.7 (19.9)
	N	18	18	18
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.2 (1.1)	**-0.9 (1.9)**	**13.2 (24.0)**
	N	17	18	17
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.1 (0.8)	**-1.2 (1.7)**	**21.7 (25.7)**
	N	16	17	16

Bold cells – Confidence interval around the change from baseline does not contain 0

4.2 Trial 002 (Drug formulation is syrup):

Fifteen patients (7 boys and 8 girls) were enrolled. Seven patients were between 5 and 7 years of age, inclusive, and 8 were between 8 and 10 years, inclusive. Greater than 70% of the patients were Caucasian. Nine patients had myelomeningocele, 2 had spinal cord injury, and the remainder are listed as having a congenital spinal cord anomaly.

Changes from baseline in urodynamic parameters are shown in Table 3.

Table 3. Study 002 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	38.4 (40.7)	119.7 (57.4)	45.6 (12.8)	58 (59.2)	81.3 (69.3)	88.7 (66.4)	2.9 (3.0)	2.7 (2.3)	2.2 (1.7)
	N	14	15	12	13	10	6	13	10	6
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	**26.7 (40.3)**	37.2 (69.8)	0 (8.4)	26.9 (73.8)	**65.3 (44.4)**	21.8 (31.7)	1.3 (3.7)	**2.2 (1.5)**	0.5 (0.8)
	N	**11**	14	10	11	7	4	11	7	4
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	**29.6 (42.3)**	40.7 (82.0)	13.3 (28.6)	**35.2 (38.2)**	33.9 (41.6)	49 (120.0)	**1.8 (1.9)**	1.1 (1.4)	1.2 (3.0)
	N	**12**	14	8	**10**	8	4	**10**	8	4
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**37.0 (55.9)**	65.0 (101.0)	2.6 (17.6)	**38.3 (83.6)**	53.1 (90.6)	86.2 (94.4)	**1.9 (4.2)**	1.8 (3.0)	2.2 (2.4)
	N	12	13	8	12	9	6	12	9	6

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary variables are shown in Table 4.

Table 4. Study 002 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	4.7 (1.4)	4.3 (1.0)	88.8 (45.9)
	N	15	14	15
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	0 (0.8)	**-0.6** **(0.8)**	7.8 (25.7)
	N	15	14	15
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.1** **(1.3)**	6.2 (25.3)
	N	14	13	14
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.3** **(1.3)**	18.9 (30.7)
	N	13	13	13

Bold cells – Confidence interval around the change from baseline does not contain 0

4.3 Trial 003 (Drug formulation is extended release capsule, Detrol LA):

Eleven patients (5 boys and 6 girls) were enrolled. Greater than 70% were Caucasian. Eight patients were between 11 and 13 years of age, inclusive, and 3 were between 14 and 15 years of age, inclusive. Eight patients had myelomeningocele, two are listed as having a congenital spinal cord anomaly, NOS, and one patient's diagnosis was unspecified.

Changes from baseline in urodynamic variables are shown in Table 5.

Table 5. Study 003 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	132.4 (76.7)	232.0 (62.7)	33.9 (15.1)	150.1 (95.4)	153.6 (47.6)	197.7 (49.0)	7.5 (4.8)	5.1 (1.6)	4.9 (1.2)
	N	11	11	9	9	5	3	9	5	3
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	25.9 (107.6)	**79.1 (90.8)**	2.0 (19.8)	72.8 (104.2)	143.7 (102.9)	134.5 (74.2)	3.6 (5.2)	4.8 (3.4)	3.4 (1.9)
	N	10	11	7	8	3	2	7	3	2
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	35.0 (59.4)	-3.8 (71.8)	5.8 (14.2)	56.0 (82.1)	22.8 (36.6)	-77.0 (28.3)	2.8 (4.1)	0.8 (1.2)	-1.9 (0.7)
	N	8	9	5	7	4	2	7	4	2
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	18.9 (114.4)	**59.4 (67.0)**	-6.4 (19.1)	45.6 (67.9)	**67.8 (61.7)**	54.0 (111.7)	2.3 (3.4)	**2.3 (2.1)**	1.4 (2.8)
	N	8	10	5	7	4	2	7	4	2

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary variables are shown in Table 6.

Table 6. Study 003 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	5.4 (1.9)	2.4 (1.8)	131.9 (48.8)
	N	11	11	11
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	-0.3 (0.9)	**-0.6** **(0.6)**	38.4 (60.4)
	N	11	**11**	11
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.7 (2.0)	**-0.9** **(0.9)**	**34.3** **(30.9)**
	N	9	**9**	9
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.9 (2.0)	**-0.7** **(0.8)**	38.5 (66.5)
	N	10	10	10

Bold cells – Confidence interval around the change from baseline does not contain 0

4.4 Comment:

Trials 001, 002, and 003 (the 3 trials in neurologically impaired children) were small, non-randomized, and not placebo controlled.

The urodynamic data from Trials 001, 002, and 003 were inconsistent across and within studies. While there were some individual variables in the two studies using tolterodine syrup that showed an apparent favorable change from baseline at some doses, only volume to first detrusor contraction, intravesical volume at 20 cm H_20, and bladder wall compliance from 0-20 cm H_20 showed a dose-response trend, and that was seen only for Study 001, which evaluated the youngest patient population.

In Trials 001, 002, and 003, there were suggestions of improvement in the number of incontinence episodes. In the 2 trials using tolterodine syrup (001 and 002), the urinary volume per micturition tended to increase at higher doses, although a dose-response trend was seen only in Study 001, which evaluated the youngest population (0-4 years). Interpretation of trends is hampered by the lack of a placebo control group.

No clear relationships between the total daily dose (by mg or by mg/kg) administered of tolterodine extended release capsules or tolterodine syrup and the PK results in pediatric patients with neurologic disease were identified.

No clear dose-response or concentration-response relationships between the dose administered of tolterodine extended release capsules or tolterodine syrup and pharmacodynamic results in pediatric patients with neurologic disease were identified.

In summary, the efficacy of tolterodine was not demonstrated in the pediatric population of neurologically impaired patients. There was a lack of consistent effect and a general lack of dose-response trends across the 3 non-randomized, non-placebo controlled studies.

5.0 Neurologically intact children

Trials 020 and 008 were randomized controlled trials that studied the effects of Detrol LA in neurologically normal children aged 5 to 10. Trial 020 was a multinational, multicenter, randomized, double-blind, placebo-controlled, 12 week treatment duration study in children with symptoms of urinary urge incontinence suggestive of detrusor instability. Patients were randomized to either Detrol LA at a fixed 2 mg/day dose or placebo in a 2:1 ratio. The Detrol LA dose was chosen after comparison of the PK of tolterodine and DD01 (the active metabolite) in children aged 5 to 10 years with adults showed that a daily total of 2 mg tolterodine immediate release in children produced exposure equivalent to that seen in adults taking a total daily dose of 4 mg tolterodine IR (both dosed bid). If the child were unable to swallow the capsule, it was opened and the beads were taken with food.

Efficacy data (diary data) were collected twice (at baseline and at week 12) for a seven-day period. Upon completion of the study, patients were eligible to enter a 12 month open label safety extension study. Unlike the trials in the neurologically impaired children, no urodynamic evaluation was performed in this trial.

Inclusion criteria included: male or female, aged 5 to 10 years inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability, defined as one or more episodes of incontinence or dampness daily during waking hours for at least 5 of 7 days, as confirmed by the run-in micturition chart.

Exclusion criteria included: 1) nocturnal enuresis or "giggle incontinence" or overactive bladder of neurologic origin 2) fewer than 2 micturitions/day during the run-in charting period 3) UTI at Visit 1, a history of urinary retention, or PVR >20% of theoretical bladder capacity on at least 2 bladder scans at Visit 2 4) severe constipation not responding to oral treatment and 5) post-menarchal females.

Trial 008 was similar in design to Trial 020, except that efficacy data (diary data) were collected at baseline and after both 4 and 12 weeks of treatment. The inclusion criteria also included a mean urinary frequency of 6 or more micturitions per 24 hours, as confirmed by the run-in micturition chart. Female patients had to be abstinent or use adequate contraception for three months prior to Visit 2 and throughout the study. Menstruating females underwent a urine pregnancy test. Like Trial 020, the study medication was Detrol LA 2 mg/day.

Efficacy results:

5.1 Trial 020:

In Trial 020, 342 patients were enrolled, with a slight male plurality. Over 90% were Caucasian. In the 5-7 year old group there were 55 placebo and 123 tolterodine treated patients; in the 8-10 year old group there were 52 placebo and 112 tolterodine treated patients.

The primary endpoint in Trial 020 was change from baseline to week 12 in the number of weekly incontinence episodes during waking hours. These efficacy results are shown in Table 7.

Table 7. Change in Weekly Incontinence Episodes

Number of Incontinence Episodes/Week	Treatment Group	
	Placebo (n = 107)	**Tolterodine PR 2 mg q.d. (n = 235)**
Missing	1	1
Baseline		
Mean (SD)	13.8 (8.0)	14.2 (9.3)
Median (min – max)	12.0 (4.0 to 46.2)	11.4 (0.0 to 60.0)
Week 12		
Mean (SD)	10.0 (8.7)	8.9 (9.1)
Median (min – max)	8.0 (0.0 to 47.0)	7.0 (0.0 to 63.0)
Change from baseline to Week 12		
Mean (SD)	-3.8 (6.1)	-5.3 (7.6)
Median (min – max)	-3.0 (-23.2 to 16.3)	-4.7 (-60.0 to 13.0)
p-value	<0.0001	<0.0001
Treatment difference		
Estimated difference in mean change (SEM)	-1.54 (0.84)	
95% confidence interval	-3.19. 0.12	
p-value	0.0689	

ITT = intent to treat; LOCF = last observation carried forward; max = maximum; min = minimum; PR = prolonged release; q.d. = once daily; SD = standard deviation; SEM = standard error of the mean.

The change from baseline was significant in both the tolterodine and the placebo arms. Comparison of the tolterodine and placebo groups, however, did not show a statistically significant difference.

The secondary endpoint, number of micturitions per 24 hours, data were not reported for the entire ITT group; rather, a subgroup analysis based on urinary frequency at baseline (7 or fewer micturitions/24 hours vs. greater than 7/24 hours) was performed. Results were not significant in either subgroup.

5.2 Trial 008:

In Trial 008, 369 patients were enrolled, with a slight male plurality. Over 90% were Caucasian. In the 4-6 year old group there were 100 tolterodine and 55 placebo treated patients, in the 7-8 year old group 106 tolterodine and 40 placebo patients, and in the 9-11 age group 46 tolterodine and 22 placebo patients.

The primary efficacy endpoint was change from baseline to week 12 in number of weekly incontinence episodes during waking hours. These efficacy results are shown in Table 8.

Table 8. Change in Weekly Incontinence Episodes

Number of Daytime Incontinence Episodes per Week		Tolterodine PR 2 mg qd (N = 252)	Placebo (N = 117)
Baseline	Mean (SD)	19.39 (13.31)	18.82 (14.07)
	Median (min – max)	16.00 (2.00 – 85.00)	14.00 (4.67 – 84.00)
	Patients not reporting (n)	1	0
Week 4	Mean (SD)	11.91 (12.71)	13.31 (12.94)
	Median (min – max)	8.00 (0.00 – 101.00)	11.00 (0.00 – 74.00)
	Patients not reporting (n)	0	0
Week 12	Mean (SD)	9.34 (11.78)	10.03 (10.06)
	Median (min – max)	5.00 (0.00 – 98.00)	7.00 (0.00 – 62.00)
	Patients not reporting (n)	0	0
Change from baseline to Week 12	Mean (SD)	–10.02 (12.15)	–8.79 (11.13)
	Median (min – max)	–9.00 (–76.00 – 18.00)	–7.00 (–49.00 – 19.00)
	Patients not reporting (n)	1	0
Difference vs. placebo after 12 weeks	Least Square Mean (SEM)	–0.88 (1.05)	
	95% CI	(–2.94, 1.18)	
	p-value	0.403	

Comparison of the change from baseline of tolterodine vs. placebo showed no statistical significance.

Mean number of daily micturitions was a secondary endpoint. The changes in mean number of daily micturitions at either week 4 or 12 were not significantly different between treatment and placebo groups.

5.3 Summary of Randomized Controlled Trials of Detrol LA in Neurologically Normal Patients with Urgency Incontinence

In children with urinary urge incontinence, statistically significant change from baseline in the primary efficacy endpoint, number of weekly daytime incontinence episodes, was not demonstrated in either Trial 020 or 008. The change in mean number of daily micturitions was not significantly different between treatment and placebo groups. Since only one dose was evaluated in these children, dose-response relationships could not be assessed.

6.0 Safety Summary

6.1 Safety Data from Submitted Trials

Safety data from eight submitted pediatric trials were reviewed. Additional information submitted by the sponsor was also reviewed, including the 2003 Annual Report and final study reports of Study 007 and 009, which were ongoing at the time of the NDA submission. Study 007 was an open-label, uncontrolled safety and efficacy study of tolterodine immediate release solution in children aged 5-10 years with urinary frequency and urge incontinence (N=142). Study 009 was a 12-month safety extension study of Study 008 (N = 318).

The database from these pediatric trials includes 1577 patients of whom 1353 were exposed to tolterodine. Only 2 of the trials (008 and 020) were placebo-controlled. Since the doses

administered did not show efficacy, the safety database may underestimate adverse events if higher doses of tolterodine are administered to children.

There were no deaths in any of the trials. Among all submitted pediatric studies, there were a total of 26 serious adverse events (SAEs) occurring in 22 subjects, 12 of which occurred in the two 12-month extension studies (021 and 009). Two of the trials included a placebo group; only two of the placebo subjects experienced an SAE. Only the 2 placebo subjects with SAE's were discontinued from the study due to the serious adverse event and the only SAE considered by the sponsor to be treatment-related was a case of pyelonephritis in a placebo patient. Reported SAE's included four urinary tract infections (UTIs), all in tolterodine-treated children, four cases of pyelonephritis, one of which was in a placebo-treated subject, and a variety of injuries and infections. With the exception of the eight cases of upper and lower tract UTI's and one case of seizures, the reviewer agrees with the sponsor that these events are unlikely to be related to tolterodine.

In the two placebo-controlled trials, events that occurred with at least twice the frequency in tolterodine vs. placebo-treated subjects were diarrhea, constipation, ear infection, abnormal behavior and rhinitis. Although not occurring at twice the placebo rate, the elevated frequency of UTIs is notable (6.6 % in subjects treated with tolterodine, 4.5% in subjects who received placebo). UTIs occurred in every study except the two studies that were of less than two weeks duration. The increase seen over placebo-treated subjects suggests that treatment with tolterodine may increase the risk of UTI. Tolterodine-treated patients had a minor increase in post-void residual urine volume; possibly this is sufficient to lead to UTI in susceptible children.

Across all pediatric trials, a total of 18 subjects manifested aggressive and/or abnormal behavior while on tolterodine. Although behavioral problems may be associated with urinary incontinence, examination of the placebo-controlled trials allows evaluation of a homogeneous population, differing only in their exposure to tolterodine. In these trials, nine tolterodine-treated patients experienced aggressive or abnormal behavior. By comparison, only one placebo subject experienced such behavior. In six tolterodine subjects, the behavior was marked enough to cause withdrawal from the trial.

6.2 Safety Information from AERS Database

In addition to the clinical trial database evaluation, the AERS data base was searched on March 2, 2004, for adverse events associated with the use of tolterodine in pediatric patients ages 0-16 years of age. Twenty-nine unduplicated cases (25 treated with Detrol tablets and 4 treated with Detrol LA capsules) aged 11 months to 16 years of age were found. Although the majority of the cases were not serious, five of these patients required hospitalization. One of these cases (breathing difficulty, laryngitis, and coughing) appeared to be plausibly related to tolterodine due to onset of symptoms five days after starting Detrol and a positive dechallenge. A second hospitalization occurred in a 12 year old child who experienced "heart block," dizziness, chest pain and fatigue while taking tolterodine and several immunosuppressive drugs. A third case involved a five-year-old hospitalized with a seizure while taking Detrol. The remaining two hospitalized cases either were associated with a plausible etiology unrelated to tolterodine or experienced a negative dechallenge.

Ten cases, in children aged five to 16 years, were events associated with CNS stimulation (aggression, hyperactivity, irritability, and insomnia). Two of these patients (both males, aged 8 and 16 years) had a history of attention deficit hyperactivity disorder (ADHD). In six patients (all males, aged 8 to 16 years) the CNS events ceased when tolterodine was discontinued. No

dechallenge information was reported for the 4 remaining cases (3 females, 1 unspecified, aged 5 to 15 years). One 8 year old male patient with a history of ADHD experienced hyperactivity that abated upon tolterodine discontinuation and reappeared after tolterodine was reintroduced.

6.3 Summary of Safety

Upon review of the available pediatric safety data, three signals of concern were noted:

- Increased frequency of UTI in subjects exposed to tolterodine
- Increased frequency of psychiatric/behavioral disorders, including aggressive behavior, seen in children treated with tolterodine. Such reports were noted both in the clinical trial data and in spontaneous case reports in the AERS database. Although data from the AERS database do not provide clear information about incidence or prevalence of adverse effects because of lack of a denominator, it is notable that about one-third of all reported pediatric cases were related to behavioral disorders, a number of which showed a positive dechallenge response. These behavioral problems may represent a CNS stimulatory reaction in children exposed to tolterodine.
- Rare reports of initiation or exacerbation of seizures in children on tolterodine, both in the clinical trial data and in the AERS database. While the treatment-relatedness of these reactions is difficult to assess, it is plausible that a CNS stimulatory effect might lower the seizure threshold and cause worsening of an existing seizure disorder.

7.0 Clinical Pharmacology:

The clinical pharmacologist reviewed two PK studies (044 and 018), two bioavailability studies (004 and 005), three PK/PD studies (001, 002, and 003), and two phase 3 efficacy studies (020 and 008). Population PK analyses conducted on data pooled from Studies 018, 044, 020, and 008 were also reviewed.

Study 004 compared the relative bioavailability of the beads from opened tolterodine extended release capsules to the intact capsules in 30 healthy adult volunteers. Although AUC for the two methods of dosing was found to be bioequivalent (for tolterodine, the active metabolite, DD 01, and the active moiety [the sum of unbound tolterodine and DD 01]), C_{max} of the three moieties was not. The beads had a 21% higher C_{max} for tolterodine than the intact capsule.

Study 005 evaluated the relative bioavailability of tolterodine immediate release and two formulations of tolterodine oral syrup in 24 healthy adult volunteers. Bioequivalence was demonstrated for DD 01 and the active moiety for both AUC and C_{max}, but was not demonstrated for tolterodine itself. The "prototype" formulation used in Studies 001 and 002 had a 19% higher tolterodine AUC and a 16% higher C_{max} than the tablet.

Review of the three PK/PD studies in children with neurogenic lower urinary tract dysfunction found no evidence of a dose-response relationship. Plotting the AUC and Cmax of both tolterodine and the active moiety against the change from baseline in volume to first detrusor contraction displayed no correlation in Trials 001, 002, or 003. An example of individual dose response data from Trial 001 is shown in Figure 1.

Figure 1. Change from Baseline in Volume to First Detrusor Contraction: Data from Study 001

(b)(4)

Study 018, which evaluated extended release tolterodine, demonstrated that, in children aged 11 to 15 years, Detrol LA produced equivalent exposure at the same dose as adults. Study 044 in 5 to 10 year old children showed that exposure in children receiving immediate release (IR) tolterodine 1 mg bid was similar to that in adults taking twice that dose, 2 mg bid, of the same formulation. Previous studies in adults have demonstrated that equivalent daily doses of tolterodine immediate release and extended release provide similar exposure. However, studies presented in this NDA submission did not show a similar relation in children between the IR and LA doses. Based on these findings, the phase 3 trials were constructed to treat 5-10 year old children with 2 mg daily of tolterodine extended release, that is half the usual adult dose.

Population PK/PD analysis using pooled data from Trials 008 and 020 indicated that the 2 mg/day dose of extended release tolterodine provided drug exposure below (31% lower) that seen in adults with 4 mg/day. A Classification and Regression Tree procedure was used to identify breakpoints in the AUC of the active moiety associated with response on the clinical outcome measure, number of incontinence episodes. Using this procedure, threshold exposure levels were identified of 12.6 nM*h in Study 020 and 14.4 nM*h in Study 008. Multivariate regression analysis showed that the two covariates predictive of clinical response were baseline frequency of incontinence and whether or not the threshold exposure had been achieved.

8.0 Conclusion:

Because efficacy was not demonstrated in either children with neurologic disease (Trials 001, 002, and 003) or neurologically normal children (Trials 008 and 020), an indication for pediatric use cannot be justified in the label. Adverse events (increased risk of urinary tract infection and behavioral disorders) which should be incorporated into the Detrol LA label were identified in the two placebo-controlled studies.

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Daniel A. Shames
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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of NDA Efficacy Supplement

Application Type	NDA
Submission Number	21-228: SE-8 Supplement No. 006
Letter Date	October 10, 2003
Stamp Date	October 14, 2003
Reviewer Name	Lisa M. Soule, MD
Review Completion Date	April 12, 2004
Established Name	NDA 21-228: Detrol LA (tolterodine tartrate) extended release capsules
Trade Name	Tolterodine tartrate
Therapeutic Class	Muscarinic receptor antagonist
Sponsor	Pfizer, Inc 7000 Portage Road Kalamazoo, MI 49001
Formulation	NDA 21-228: Extended release capsules
Approved Indication	Detrol LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
Related NDAs/INDs	NDA 20-771 (Detrol) IND 56,406 (Detrol LA) IND 46,169 (Detrol)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Approvability

It is recommended that the efficacy supplement for NDA 21-228 (SE8-006) receive an **Approval.**

1.1.1 Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

The clinical findings in the NDA efficacy supplement electronically submitted on October 10, 2003 to NDA 21-228 (Detrol LA) as SE8-006, are summarized as follows:

- Studies (001, 002, and 003) in children with neurogenic lower urinary tract dysfunction were small, non-randomized, non-placebo-controlled trials. The urodynamic data from these trials were inconsistent and there was a general lack of dose-response trends. There were suggestions of improvement in the number of incontinence episodes in the tolterodine-treated groups
- In Studies 020 and 008 using Detrol LA (prolonged release tolterodine) in children with urinary urge incontinence, statistically significant change from baseline in the primary efficacy endpoint, weekly number of daytime incontinence episodes, was not demonstrated in either trial. Number of micturitions per 24 hours, a secondary endpoint, in the tolterodine groups was also not significantly different from the placebo groups.
- Safety signals suggesting increased incidence of urinary tract infections and paradoxical CNS stimulation/agitation with tolterodine treatment were identified.

Following the review of the NDA efficacy supplement, the clinical reviewer has reached the following conclusions:

- Studies in neurologically impaired children aged 3 months to 10 years (Studies 001 and 002) were performed with a non-commercially available syrup formulation. Efficacy was not established based on urodynamic and clinical data from these small, non-controlled studies.
- Administration of tolterodine prolonged release (PR) capsules for up to 12 weeks failed to support efficacy as measured by improvement of urodynamic parameters nor in demonstrating a statistically significant dose-response trend in reduction of incontinence episodes in 11 pediatric patients with spina bifida aged 11 to 15 years (Study 003).
- Two large, randomized, placebo-controlled trials failed to support the efficacy of tolterodine PR capsules for the treatment of urinary urge incontinence in neurologically normal pediatric patients (Studies 020 and 008).
- No clear relationship between the total daily dose (by mg or by mg/kg) administered of tolterodine PR capsules or tolterodine syrup and the pharmacokinetic results in pediatric patients with myelomeningocele were identified.
- No clear dose-response or concentration-response relationships between the total daily dose administered of tolterodine PR capsules or tolterodine syrup and pharmacodynamic results in pediatric patients with myelomeningocele were identified.
- Studies in neurologically normal children with urinary urgency, frequency and urge incontinence evaluated only a single dose of tolterodine, so dose-response relationships were not obtained.
- The sponsor proposed no changes to the Detrol labeling.
- The sponsor proposed changes to the Clinical Pharmacology, Clinical Studies, Precautions, and Adverse Reactions sections of the Detrol LA labeling. The clinical reviewer recommends that labeling changes be included only in the Pediatric Use Subsection of the Precautions Section.

The labeling would note that efficacy has not been demonstrated in a pediatric population, would describe the two randomized, placebo-controlled studies that were conducted in neurologically normal children, and would note specific safety concerns arising from those studies.

1.2 Recommendations on Post-Marketing Actions

Not applicable

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

Tolterodine tartrate is a competitive muscarinic receptor antagonist first approved as immediate release tablets on March 25, 1998. It is currently available from the sponsor in two different formulations: Detrol tablets (1 and 2 mg immediate release tablets) and Detrol LA (2 and 4 mg extended release capsules). Detrol LA was approved on December 22, 2000.

Interest in additional therapeutic options for pediatric patients led to issuance of a Written Request for studies of tolterodine in children with neurogenic lower urinary tract dysfunction and in neurologically normal children with symptoms of urinary frequency, urgency and urge incontinence. The Written Request was issued to the sponsor on January 23, 2001, requesting three clinical trials in pediatric patients with detrusor hyperreflexia due to neurogenic conditions such as spina bifida, one trial in neurologically normal pediatric patients with urinary frequency, urgency and urge incontinence, and two critical analyses. On October 10, 2003, the sponsor responded to the Written Request by submitting electronically an NDA supplement to Detrol LA (NDA 21-228), which was referenced to the Detrol NDA, 20-771. The supplement contained final study reports for six studies which responded to the Written Request, four additional studies and two critical analyses.

The Division of Reproductive and Urologic Drug Products (DRUDP or HFD-580) compared the six submitted pediatric study reports and the two submitted critical analyses with the requirements listed in the Written Request and presented their findings to the Pediatric Exclusivity Board on January 5, 2004. The Pediatric Exclusivity Board determined that Pfizer's submission SE8-006 fairly responded to the Written Request and recommended granting a six month extension of all remaining exclusivity and patents for both of the Sponsor's tolterodine formulations.

This current review was performed to determine if the data from the six clinical studies support the sponsor proposed pediatric labeling changes submitted in the NDA supplement regarding the pharmacokinetic properties and efficacy and safety of the Detrol LA formulation. In the supplement, the sponsor claims that the submitted clinical trial data demonstrate the safety of Detrol LA capsules for pediatric patients, while noting that efficacy has not been demonstrated in the clinical trials. Based on these data, the sponsor proposes the addition of pediatric pharmacokinetic data and a description of adverse events seen in children exposed to Detrol LA.

1.3.1.1 Design of the Six Clinical Studies Responding to the Pediatric Written Request

Study 583E-URO-0581-001. This was a Phase 1/2 multicenter, 12-week treatment duration, open label, dose escalating (0.03, 0.06 and 0.12 mg/kg/day), pharmacokinetic, pharmacodynamic (urodynamic), clinical effect and safety study of tolterodine oral solution in 19 pediatric subjects with detrusor hyperreflexia due to neurogenic conditions. Subjects were aged 1 month to 4 years, inclusive. Pharmacokinetic parameters for the active moiety, tolterodine and the major metabolite DD 01 were determined in 17 patients at the mid-range dose (0.06 mg/kg/day). Pharmacodynamic (urodynamic) variables and patient diary variables were assessed at each dose level. Dose-effect of tolterodine and concentration-effect of the active moiety were determined at the mid-range dose.

Study 583E-URO-0581-002. This was a Phase 1/2 multicenter, 12-week treatment duration, open label, dose escalating (0.03, 0.06 and 0.12 mg/kg/day), pharmacokinetic, pharmacodynamic (urodynamic), clinical effect and safety study of tolterodine oral solution in 15 pediatric subjects with detrusor hyperreflexia due to neurogenic conditions. Subjects were aged 5 to 10 years, inclusive. Pharmacokinetic parameters for the active moiety, tolterodine and DD 01 were determined at the mid-range dose (0.06 mg/kg/day). Pharmacodynamic (urodynamic) variables and patient diary variables were assessed at each dose level. Dose-effect of tolterodine and concentration-effect of the active moiety were determined at the mid-range dose.

Study 583E-URO-0581-003. This was a Phase 1/2 multicenter, 12-week treatment duration, open label, dose escalating (2 mg, 4 mg and 6 mg/day), pharmacokinetic, pharmacodynamic (urodynamic), clinical effect and safety study of tolterodine extended release capsules in 11 pediatric subjects with detrusor hyperreflexia due to neurogenic conditions. Subjects were aged 11 to 15 years, inclusive. Pharmacokinetic parameters for the active moiety, tolterodine and DD 01 were determined at the mid-range dose (4 mg/day). Pharmacodynamic (urodynamic) variables and patient diary variables were assessed at each dose level. Dose-effect of tolterodine and concentration-effect of the active moiety were determined at the mid-range dose.

Study 583E-URO-0084-020. This was a Phase 3 multicenter, 12-week treatment duration, randomized, double-blind placebo-controlled (2:1 ratio), clinical effect, pharmacokinetic and safety study of tolterodine extended release capsules in 342 pediatric subjects with symptoms of urinary urge incontinence suggestive of detrusor instability. Subjects were aged 5 to 10 years, inclusive. The dose of tolterodine was 2 mg/day. Efficacy was assessed by change from baseline in number of incontinence episodes/week.

Study DETAPE-0581-008. This was a Phase 3 multicenter, 12-week treatment duration, randomized, double-blind placebo-controlled (2:1 ratio), clinical efficacy and safety study of tolterodine extended release capsules in 369 pediatric subjects with symptoms of urinary urge incontinence suggestive of detrusor instability with at least 6 micturitions/24 hours. Subjects were aged 5 to 10 years, inclusive. The dose of tolterodine was 2 mg/day. Efficacy was assessed by change from baseline in number of incontinence episodes/week. Population pharmacokinetic/pharmacodynamic data were also evaluated.

Study 583E-URO-0084-021. This was a Phase 3 multicenter, 12-month treatment duration, open label safety, tolerability and clinical efficacy study of tolterodine extended release capsules in 298 pediatric subjects with symptoms of urinary urge incontinence suggestive of detrusor instability, aged 5 to 15 years, inclusive. The subjects were previously enrolled in Study 020 (298 patients aged 5-10 years) or Study 018 (27 patients aged 11-15 years). The dose of tolterodine was 2 mg/day. The primary endpoint was incidence, duration and intensity of adverse events during 12 months of treatment. Clinical efficacy was also assessed.

1.3.1.2 Design of the Four Additional Clinical Studies

Study 583E-URO-0581-004. This was a Phase 1 open-label, randomized single-dose crossover study of the relative bioavailability of the beads from opened tolterodine extended release capsules and the intact capsules in 30 healthy adult volunteers. The primary endpoints were the $AUC_{0\text{-infinity}}$ and C_{max} ratios for the active moiety from the beads sprinkled over applesauce relative to the intact capsules.

Study 583E-URO-0581-005. This was a Phase 1 open-label, randomized single-dose crossover study of the relative bioavailability of two formulations of tolterodine liquid and tolterodine immediate release tablets in 24 healthy adult volunteers. The primary endpoints were the $AUC_{0\text{-infinity}}$ and C_{max} ratios for tolterodine and DD 01 from the liquid formulations relative to the immediate release tablets.

Study 583E-URO-0084-018. This was a Phase 1 open-label, 7-day treatment duration, dose-escalation pharmacokinetic and safety study of two doses of tolterodine extended release capsules in

31 pediatric subjects with urinary urge incontinence, aged 11 to 15 years. The primary endpoint was the AUC_{0-24} for the active moiety. Additional pharmacokinetic variables, effect and safety of tolterodine were studied secondarily.

Study 97-OATA-044. This was a Phase 1 open-label, 14-day treatment duration, dose-escalation pharmacokinetic and safety study of three doses of tolterodine immediate release tablets in 33 pediatric subjects with urinary urge incontinence, aged 5 to 10 years. The primary endpoint was the postvoid residual urinary volume assessed by ultrasound after 2 weeks of treatment. Efficacy, additional safety assessments and pharmacokinetic data were studied secondarily.

1.3.2 Efficacy

1.3.2.1 Efficacy in Neurogenic Bladder

Efficacy Endpoints

There was no pre-specified primary efficacy endpoint in the three studies in patients with neurogenic lower urinary tract dysfunction, and these studies were not placebo controlled. A variety of clinical effect endpoints were evaluated, including both urodynamic variables and variables derived from patient diaries completed toward the end of each treatment. These limitations, and the fact that there were no pre-determined criteria as to what would be judged a clinically meaningful change in any of the endpoints, make determination of efficacy difficult.

Efficacy Results

In the three studies of neurogenic lower urinary tract dysfunction, there were no consistent trends indicating efficacy of tolterodine treatment. Methodological limitations as noted above and very small sample sizes make it difficult to evaluate the relevance of the changes observed from baseline. The sponsor did not conduct hypothesis testing in these three studies; thus, no p-values were provided in the study reports. The statistical reviewer provided an analysis of the change from baseline and test of trend for a dose-response effect. The magnitude of the changes described below is based on mean change in the value at each dose period. The following variables showed statistically significant changes from baseline values:

Study 001 (N=19)

- Volume to first detrusor contraction increased by 34 ml at the highest dose level
- Functional bladder capacity increased by 32 ml at the middle dose level
- Intravesical volume at 20 cm H_20 increased by 37 ml at the middle dose level and by 29 ml at the highest dose level
- Bladder wall compliance at 0-20 cm H_20 increased by 1.9 ml/cm H_20 at the middle dose level and by 1.5 ml/cm H_20 at the highest dose level
- Mean number of daily incontinence episodes decreased by 0.9 voids in the middle dose level and by 1.2 voids in the highest dose level
- Mean volume per void increased by 13 ml in the middle dose level and by 22 ml in the highest dose level

Study 002 (N=15)

- Volume to first detrusor contraction increased by 27 ml at the lowest dose level, by 30 ml at the mid-dose level and by 37 ml at the highest dose level
- Functional bladder capacity increased by 41 ml at the middle dose level and by 65 ml at the highest dose level

- Intravesical volume at 20 cm H_20 increased by 35 ml at the middle dose level and by 38 ml at the highest dose level
- Intravesical volume at 30 cm H_20 increased by 65 ml at the lowest dose level
- Bladder wall compliance at 0-20 cm H_20 increased by 1.8 ml/cm H_20 at the middle dose level and by 1.9 ml/cm H_20 at the highest dose level
- Bladder wall compliance at 0-30 cm H_20 increased by 2.2 ml/cm H_20 at the lowest dose level
- Mean number of daily incontinence episodes decreased by 0.6 voids in the lowest dose level, by 1.1 voids in the middle dose level and by 1.3 voids in the highest dose level
- Mean volume per void increased by 19 ml in the highest dose level

Study 003 (N=11)

- Functional bladder capacity increased by 79 ml at the lowest dose level and by 59 ml at the highest dose level
- Mean number of daily incontinence episodes decreased by 0.6 voids in the lowest dose level, by 0.9 voids in the middle dose level and by 0.7 voids in the highest dose level

In summary, consistent results across the three studies indicate that there is little benefit at the lowest dose. Changes seen in the middle and higher dose level groups were generally greater, but inconsistent as to whether the middle or the highest dose provided the greater benefit. Generally, clear dose-response trends were not demonstrated. There did appear to be a consistent improvement in the number of daily incontinence episodes, at least at the two higher dose levels, and in a dose-response manner in two of the three trials. Improvement in the greatest number of variables with the most frequent dose-response trends was shown in Study 001, using tolterodine syrup in subjects aged 3 months to four years.

Medical Reviewer Comment:

The lack of a consistent effect across the three studies, the general lack of dose-response trends and the lack of a placebo control leads this reviewer to conclude that efficacy of tolterodine in a pediatric population suffering from urinary incontinence related to neurogenic lower urinary tract dysfunction has not been demonstrated.

1.3.2.2 Efficacy in Urinary urge incontinence

Efficacy Endpoints

The primary efficacy endpoint in both Studies 020 and 008 was change from baseline to week 12 in the number of daytime incontinence episodes per week. A number of secondary efficacy endpoints were evaluated at week 12 in both studies, and after four weeks of treatment in Study 008.

Efficacy Results

Neither Study 020 nor 008 demonstrated a statistically significant change in the number of weekly incontinence episodes after 12 weeks of treatment. In Study 020, the tolterodine group showed a decrease that was 1.5 weekly episodes greater than that seen in placebo subjects (p=0.07). In Study 008, the tolterodine group had a decrease of 1.2 episodes per week more than that seen in placebo subjects (p=0.4).

Excluding exploratory subgroup analyses, the only statistically significant findings in Study 020 were:

- a greater increase in volume per micturition (7.9 ml per micturition more in tolterodine-treated than placebo subjects, p=0.03) and
- a 15% higher perception of treatment benefit among parents of those children treated with tolterodine as compared to placebo (p=0.01).

In Study 008, there was similarly a statistically significantly greater increase in volume per micturition as compared to baseline in the tolterodine group at both four and twelve weeks, respectively; 6.6 ml/void and 9.1 ml/void greater than seen in placebo subjects (p=0.047 at four weeks, p=0.02 at 12 weeks). There were also significantly greater improvements in three of ten questions in the Treatment Satisfaction Questionnaire (quality of life, improvement in symptoms and satisfaction with outcome); however, these statistical analyses were not adjusted for multiple comparisons.

Medical Reviewer's Comments:

1) **The sponsor did not report results from the ITT population for the secondary efficacy variable volume per micturition in Study 020. The statistically significant result reported is based upon the Statistics reviewer's analysis of the sponsor's data.**
2) **The reviewer concludes that efficacy of tolterodine in a neurologically normal pediatric population with urinary urge incontinence has not been demonstrated. This conclusion is based on the fact that neither study demonstrated statistically significant improvement from baseline as compared to placebo in the primary efficacy endpoint, and that the only secondary endpoints with statistically significant change (small increase in volume per micturition, some degree to greater parental satisfaction with treatment) are of doubtful clinical significance.**

1.3.3 Safety

No deaths occurred in any of the trials. Twenty-six serious adverse events occurred in 22 subjects, but with the exception of eight cases of upper and lower urinary tract infections and one case of seizures, the reviewer agrees with the sponsor that these events are unlikely to be related to tolterodine. Three signals of concern were noted:

- Increased frequency of UTI in subjects exposed to tolterodine, which may be related to the increased postvoid residual volume seen in exposed subjects in several trials.
- Increased frequency of psychiatric/behavioral disorders, particularly aggressive behavior, seen in children treated with tolterodine. Such reports were noted both in the clinical trial data and in spontaneous case reports in the AERS database. Although data from the AERS database cannot be thought to describe incidence or prevalence of adverse effects, it is notable that about one-third of all reported pediatric cases related to behavioral disorders, a number of which showed a positive dechallenge response. These behavioral problems may represent a paradoxical CNS agitation reaction in children exposed to tolterodine.
- There are rare reports of initiation or exacerbation of seizures in children on tolterodine, both in the clinical trial data and in the AERS database. The treatment-relatedness of these reactions is difficult to assess.

1.3.4 Dosing Regimen and Administration

No specific recommendations for dosing regimens in children are proposed by the sponsor. The formulation tested that is commercially available, Detrol LA, failed to show efficacy in children.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in this efficacy supplement.

1.3.6 Special Populations

In the neurogenic populations studied, sample sizes were too small to allow evaluation of the effects of gender, race, age or weight subgroups or metabolizer status. Review of the adverse effects experienced by the five poor metabolizers in these three studies does not reveal any indication of increased frequency or severity of adverse effects.

In the two studies evaluating urinary urge incontinence, subgroups based on race were not evaluated, due to the small numbers of non-Caucasians. Metabolizer status was not evaluated in the assessment of efficacy or safety; however, review of the adverse effects experienced by the 16 poor metabolizers identified in these two studies does not reveal any indication of increased frequency or severity of adverse effects. Subgroup analyses of gender, age and weight groups were performed. Study 020 found significantly increased efficacy as measured by the primary endpoint in children between 4-6 years of age and in males, although this measure may be influenced by the lesser change experienced by the placebo group in these gender and age subgroups.

Safety was also evaluated with respect to gender, age and weight subgroups. In Study 020, the oldest and heaviest subgroups experienced a lower frequency of adverse events in the tolterodine group as compared to placebo, which may represent the effect of decreased drug exposure in these subgroups. Study 008 showed a higher frequency of adverse events, particularly UTIs, in females, in both tolterodine and placebo-treated subjects. The frequency of adverse events decreased with increasing age group in both treatment groups. The lowest weight subgroup (<20 kg) had a higher incidence of adverse events in the tolterodine group, as compared to placebo and to tolterodine-treated subjects in the two higher weight groups. Again, this may represent association of greater numbers of adverse events with higher drug exposure.

CLINICAL SUMMARY

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Tolterodine tartrate is a competitive muscarinic receptor antagonist first approved as immediate release tablets in 1998. It is currently available in two different formulations: Detrol tablets (1 and 2 mg immediate release tablets) and Detrol LA (2 and 4 mg extended release capsules).

2.2 State of Armamentarium for Indications

Ditropan (oxybutynin chloride), a muscarinic antagonist, was approved for marketing in 1975, and is available in tablet and syrup formulations. Ditropan XL obtained a pediatric indication in 2003 for the treatment of symptoms of detrusor overactivity due to neurogenic conditions (e.g. myelomeningocele) in children 6 years and older.

2.3 Availability of Proposed Product in the U.S.

The product is currently available as Detrol (immediate release) 1 mg and 2 mg tablets and Detrol LA (extended release) 2 mg and 4 mg capsules. An oral solution is not commercially available.

2.4 Important Issues with Pharmacologically Related Products

Terodiline, a closely related chemical structure, was approved in Europe and later withdrawn for safety reasons. It was found to have calcium channel blocking properties and to increase the QT

interval and induce torsade de pointes in humans. A consult in 2002 by the Division of Cardio-Renal Drug Products concerning tolterodine found that in nonclinical models of QT prolongation, the parent compound and its metabolites blocked HERG current in a concentration-related manner. Human QT studies evaluating tolterodine are in progress.

2.5 Pre-submission Regulatory Activity

NDA 20-771 was submitted for Detrol tablets on March 24, 1997, by Pharmacia & Upjohn and it was approved on March 25, 1998.

NDA 21-228 was submitted for Detrol LA extended release capsules on February 25, 2000, by Pharmacia & Upjohn and it was approved on December 22, 2000.

Discussions with Pharmacia & Upjohn regarding pediatric exclusivity and labeling date back to 1999. The sponsor submitted a pediatric written request proposal on June 28, 2000, under NDA 21-228. FDA then issued a Written Request letter dated January 23, 2001, asking Pharmacia & Upjohn to perform four pediatric studies with tolterodine tartrate and to prepare two critical analyses. The Written Request was amended on four occasions. On October 16, 2003, the sponsor responded to the Written Request by submitting electronically an efficacy supplement to NDA 21-228, referenced to NDA 20-771. The sponsor at this time is Pfizer Inc, which acquired Pharmacia on April 16, 2004. The NDA supplement contained final study reports for six studies which respond to the Written Request, four additional studies and two critical analyses.

The Division of Reproductive and Urologic Drug Products (DRUDP or HFD-580) compared the six submitted pediatric study reports and the two submitted critical analyses with the requirements listed in the Written Request and presented their findings to the Pediatric Exclusivity Board on January 5, 2004. The Pediatric Exclusivity Board determined that Pfizer's submission SE8-006 fairly responded to the Written Request and recommended granting a six month extension of all remaining exclusivity and patents for both of the sponsor's tolterodine formulations.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DIVISIONS

3.1 Chemistry Review

Chemistry review was not conducted since tolterodine tablets and capsules are approved drug products and no new CMC information was submitted. No CMC information was submitted for the oral solution.

3.2 Animal Pharmacology/Toxicology Review

New toxicological data were not submitted and toxicology review was not conducted since tolterodine tablets and capsules are approved drug products.

3.3 Clinical Pharmacology Review

The Clinical Pharmacology reviewer examined the sponsor's two PK studies (044 and 018), two relative bioavailability studies (004 and 005), three PK/PD studies (001-003) and two phase 3 efficacy studies (020 and 008), as well as the population PK analyses conducted on data pooled from Studies 018 and 044 and from Studies 018, 044, 020 and 008.

Previous studies in adults have demonstrated that equivalent daily doses of tolterodine immediate release and prolonged release provide similar exposure (i.e., 2 mg BID Detrol was equivalent to 4 mg Detrol LA daily). Study 044, in 5-10 year old children, showed that exposure in children receiving immediate release tolterodine 1 mg BID was similar to that in adults taking 2 mg BID of the same formulation. Study 018, in children 11-15 years, evaluated prolonged release tolterodine and showed that this older pediatric population showed equivalent exposure at the same dose as adults. Based on

these findings, the phase 3 trials were constructed to treat 5-10 year old children with 2 mg daily of tolterodine extended release, half the usual adult dose.

However, while Study 001, in children aged 3 months to 4 years, found that an average daily dose of 0.7 mg produced active moiety exposures equivalent to adults taking 2 mg BID, Study 002, in 5-10 year olds, found that an average dose more than double that used in the younger children (1.66 mg/day), produced exposures only half that of adults taking 2 mg BID. This Study 002 result also contrasted with results obtained with children of the same age in Study 044, the primary difference between the studies being the formulation used (immediate release tablets in adults and Study 044, immediate release oral solution in Studies 001 and 002). Study 003, in which 11-15 year olds received tolterodine prolonged release, found that the 4 mg/day dose produced exposures similar to those in adults receiving the same dose.

Review of the three PK/PD studies in subjects with neurogenic lower urinary tract dysfunction found no evidence of a dose-response relationship. Plotting the AUC and the C_{max} of both tolterodine and the active moiety against the change from baseline in volume to first detrusor contraction displayed no correlation in Study 001, 002 or 003.

The sponsor conducted two phamacometric analyses, the first using rich data from Studies 018 and 044. Sparse data from Studies 008 and 020 were then incorporated into the model developed from the first analysis. In the initial analysis, because two different aged populations were exposed to two different formulations (tolterodine immediate release in the 5-10 year olds and tolterodine prolonged release in the 11-15 year olds), the effects of age and formulation are confounded. A three-compartment PK model best fit the data from Studies 018 and 044 (drug depot, tolterodine and DD 01).

Population PK/PD analysis using pooled data from Studies 008 and 020 (weighted toward 008, as 68% of the data came from that study) indicated that the selected dose of 2 mg/day of extended release tolterodine provided drug exposure below that seen in adults dosed with 4 mg daily, particularly for the heavier children (>25 kg). A Classification and Regression Tree procedure was used to identify breakpoints in the AUC of the active moiety associated with response on the clinical outcome measure, number of incontinence episodes. Using this procedure, threshold exposure levels were identified of 12.6 nM*h in Study 020 and 14.4 nM*h in Study 008. Multivariate regression analysis showed that the two covariates predictive of clinical response were baseline frequency of incontinence and whether the threshold exposure had been achieved.

The clinical pharmacology reviewer concluded that statistically significant efficacy of tolterodine was not shown in the phase 3 studies. The reviewer noted that the dose chosen for these studies, 2 mg of tolterodine prolonged release capsules, may have been low, as suggested by the population PK studies.

3.4 Statistics Review

The statistical review focused on the two randomized controlled trials conducted in the population with urinary urgency, frequency and incontinence (Studies 020 and 008). It was noted that the primary efficacy analysis specified in each protocol was an intent-to-treat (ITT) analysis, with missing data on micturition charts imputed by the last observation carried forward (LOCF) technique. Both studies were powered to detect a difference of five incontinence episodes per week between tolterodine and placebo groups with a power of 80% and a two-tailed significance level of 0.05%. Study 020 was analyzed using analysis of variance (ANOVA) with change from baseline in the efficacy variables estimated within and compared between treatment groups. Study 008 was analyzed using analysis of covariance (ANCOVA), adjusting for the covariates baseline urinary frequency, country and treatment-by-country interaction, as well as assessing treatment effect. No statistical adjustments for multiple comparisons were made.

The statistician noted that use of LOCF in Study 008 was acceptable, as there was less than 7% study withdrawal. In study 020, 20-23% of the population either withdrew or had absent micturition chart data, making imputation of data by LOCF more problematic. For both studies, the statistical reviewer confirmed the ITT analysis done by the sponsor, and also performed Per Protocol (PP, defined as those subjects who did not withdraw from the study and who had no major protocol violations) and Completer (defined as those subjects who had no missing data for the micturition chart) analyses as added sensitivity tests. In study 020, the reviewer also analyzed the data for the ITT population minus subjects from the UK, since there were possible differences in the definition of the primary efficacy endpoint between UK and non-UK subjects.

Review of demographic and baseline characteristics in each study found them to be well-balanced across treatment groups. Differences between tolterodine and placebo groups on frequency of having had prior efficacy in medical treatment for urinary urge incontinence (among those with prior treatment) were not statistically significant. Evaluation of the PP and Completer populations found them comparable to the ITT population.

On the primary efficacy endpoint, change from baseline to week 12 in number of daytime incontinence episodes/week, both studies showed decreases in the tolterodine group that were greater than those seen in the placebo group (between-group difference of -1.5 episodes/week in Study 020 and -0.9 episodes/week in Study 008); however, in neither study did this difference achieve statistical significance. Consideration of PP and Completer populations, and analysis using a non-parametric statistic did not alter these results.

Analysis of the secondary efficacy endpoints, which differed slightly between the two studies, did find some statistical evidence of efficacy in some of the variables. In Study 020, there was a statistically significant difference between treatment groups in the mean urinary volume per micturition, with the tolterodine mean exceeding that in the placebo group by 8 ml. Parental perception of treatment benefit was also significantly greater in the tolterodine group, with 15% more than in the placebo group finding benefit. In Study 008, mean urinary volume per micturition was again significantly different between groups, at both four weeks (6.6 ml greater in the tolterodine group) and 12 weeks of treatment (9.2 ml greater in the tolterodine group). Three of ten items on the treatment satisfaction questionnaire were significantly better in the tolterodine group: satisfaction with treatment outcomes, change in symptoms and change in overall quality of life.

Extensive subgroup analyses of the primary and secondary efficacy endpoints were conducted by the sponsor and by the statistical reviewer and are detailed in the Statistics Review. The major findings are indications of significantly greater efficacy on the primary endpoint among tolterodine-treated children between ages 4-6, with weight <= 35 kg and in males. These analyses are considered exploratory in nature, and do not affect the recommendations concerning efficacy labeling. Overall, the statistics reviewer concluded that the efficacy of tolterodine in the pediatric population with urinary frequency and urge incontinence has not been demonstrated.

3.5 Office of Drug Safety Review

The Division of Drug Risk Evaluation (DDRE) in the Office of Drug Safety conducted a search of the AERS database to identify reported adverse events associated with the use of Detrol and Detrol LA in children aged 16 and under as of March 2004. Twenty-nine unduplicated case reports were found, including five involving hospitalizations. Of the hospitalizations, one involved breathing difficulties, nocturnal laryngitis and coughing, which began within five days of the start of tolterodine treatment, and resolved with discontinuation of the drug. A second hospitalization occurred in a child who experienced "heart block" (not further specified), dizziness, chest pain and fatigue while taking tolterodine and several immunosuppressive drugs; the heart block resolved with discontinuation of tolterodine, but the remaining symptoms did not. A third case involved a five-year-old hospitalized with a seizure while taking Detrol. The time from initiation of medication is unknown. The

remaining two hospitalized cases either were associated with a plausible etiology unrelated to tolterodine or demonstrated a negative dechallenge.

A total of 19 case reports involved anticholinergic effects, with nine cases reporting classic effects such as urinary retention, constipation, flushing, dry mouth and blurred vision, eight reporting symptoms suggesting paradoxical CNS stimulatory effects (aggression, hyperactivity, irritability, insomnia) and two reporting both classes of effects. In six of the cases of CNS stimulation, all in males, a positive dechallenge was reported; in the remaining four cases, all in females, dechallenge information was not provided. Urinary tract infection was reported in two cases; however, in neither was it attributed to tolterodine.

DDRE noted that some of the anticholinergic effects noted in children are currently unlabeled, including confusion, overheating and flushing. The Division recommends that these, as well as the paradoxical CNS stimulation, be added to the Detrol and Detrol LA labels.

The Office of Drug Safety also conducted a search of three IMS databases to estimate the extent of off-label use of tolterodine in children. An estimate of between prescriptions written in 2003 for children under 17 was made. Approximately of these were for Detrol LA, the remainder for Detrol tablets. Almost of prescriptions were for children aged 12 and above, with of use in children aged 2 to 11 years.

3.6 DDMAC Review

The Division of Drug Marketing, Advertising and Communications (DDMAC) made three comments about the proposed labeling submitted for Detrol LA. They requested that the discussion of pediatric studies in the three sections, Pharmacokinetics in Special Populations, Clinical Studies and Adverse Reactions, be deleted in order to avoid an implication of efficacy in the pediatric population. They recommended that, if clinically relevant, safety information be included in the section Precautions – Pediatric Use, along with a prominent statement about Detrol LA's lack of efficacy in this population. Finally, they requested that statements about adverse events being "higher" or "lower" in a given population be qualified and put into context.

4 DATA SOURCES, REVIEW STRATEGY AND DATA INTEGRITY

4.1 Sources of Clinical Data

4.1.1 Clinical Trial 583E-URO-0581-001

The sponsor submitted the final study report 583E-URO-0581-001 [*5.3.4.2.1*] to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated August 5, 2002 and March 3, 2003, for Study #1.

4.1.2 Clinical Trial 583E-URO-0581-002

The sponsor submitted the final study report 583E-URO-0581-002 [*5.3.4.2.2*] to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated August 5, 2002, March 3, 2003 and October 8, 2003, for Study #3.

4.1.3 Clinical Trial 583E-URO-0581-003

The sponsor submitted the final study report 583E-URO-0581-003 [*5.3.4.2.3*] to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated August 5, 2002 and March 3, 2003, for Study #1.

4.1.4 Clinical Trial 583E-URO-0084-020

The sponsor submitted the final study report 583E-URO-0084-020 [*5.3.5.1.1*] along with study report 583E-URO-0084-021 to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated November 15, 2001, August 5, 2002 and March 3, 2003, for Study #4.

4.1.5 Clinical Trial DETAPE-0581-008

The sponsor submitted the final study report DETAPE-0581-008 [*5.3.5.1.4*] to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated November 15, 2001, August 5, 2002 and March 3, 2003, for Study #4.

4.1.6 Clinical Trial 583E-URO-0084-021

The sponsor submitted the final study report 583E-URO-0084-021 [*5.3.5.1.3*] along with study report 583E-URO-0084-020 [*5.3.5.1.1*] to meet the requirements listed in the Written Request dated January 23, 2001, with amendments dated November 15, 2001, August 5, 2002 and March 3, 2003, for Study #4.

4.1.7 Critical Analyses

The sponsor submitted one module [*5.3.5.4.1*] to meet the two critical analyses requirements listed in the Written Request dated January 23, 2001. The report was entitled "Critical Analysis of Adult Urodynamic Studies and Literature Review."

4.2 Table of Clinical Studies

In total, this efficacy supplement provided reports of ten studies, six of which were in response to the Written Request, and four that were additional studies. Safety data were also provided from an additional two studies which were completed following submission of the efficacy supplement.

Two studies were bioavailability studies; Study 005 compared two oral solution formulations with the immediate release (IR) tablet, and Study 004 compared intact prolonged release (PR) capsules with the beads from opened PR capsules sprinkled on applesauce. Two clinical pharmacology studies were conducted; Study 044, which compared three doses of tolterodine IR in 5-10 year olds with urinary frequency and/or urge incontinence, and Study 018, which compared two doses of tolterodine PR in 11-15 year olds with urinary urgency and frequency and/or urge incontinence The six studies submitted in response to the Written Request, as previously detailed, include two randomized, double-blind, placebo-controlled clinical trials in children ages 5-10 with urinary urge incontinence, and one extension study of this population (Studies 020, 008 and 021), and three uncontrolled, non-randomized, dose escalation studies in children with neurogenic lower urinary tract dysfunction in three age groups, ranging from 3 months to 15 years of age.

Table 1 provides a more detailed overview of each clinical trial represented in the supplement, including information regarding the study design, the drug formulation evaluated, number of patients enrolled and study treatments.

Table 1 Tabular Listing of Submitted Clinical Investigations

Type of Study	Study ID	Location of Study Report	Objectives of Study	Study Design & Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status: Type of Report
BA	005	[5.3.1.2.1]	Compare BA of 2 OS formulations with IR tablet	3-way crossover	Flavored colored OS 1 mg/5 mL, 4 mg SD, PO Flavored OS 1 mg/5 mL, 4 mg SD, PO IR tablet 2 mg 4 mg SD, PO	24	Healthy subjects	Single dose	Complete Full
BA	004	[5.3.1.2.2]	Compare BA of PR capsule contents (beads) sprinkled on applesauce with PR capsule (intact)	2-way crossover	PR capsule 4 mg (intact or opened), 8 mg SD, PO	30	Healthy subjects	Single dose	Complete, Full
PK/PD	044	[5.3.3.2.3]	PK, safety, and clinical effect in children 5-10 years of age	Open-label, 3 escalating dose groups	IR tablet 0.5, 1, or 2 mg bid PO	33 (30 PK)	Patients with urinary frequency/urge incontinence	14 days	Complete Full
PK/PD	018	[5.3.3.2.1]	PK, safety, and clinical effect in children 11-15 years of age	Open-label, 2 escalating dose groups	PR capsule, 2 mg or 4 mg qd, PO	31 (29 PK)	Patients with overactive bladder	6-10 days	Complete, Full
PK/PD	001	[5.3.4.2.1]	PK	Open-label, multicenter dose-escalation, uncontrolled	MD Tolt liquid PO 1 mg/5 mL mg/kg/d bid 0.03 x 4 wk 0.06 x 4 wk 0.12 x 4 wk	19 safety 17 PK	Neurological disease Age 1 mo – 5 y	12 wk	Complete Full
PK/PD	002	[5.3.4.2.2]	PK	Open-label, multicenter dose-escalation uncontrolled	MD Tolt liquid PO 1.0 mg/5 mL mg/kg/d bid 0.03 x 4 wk 0.06 x 4 wk 0.12 x 4 wk	15 safety/PK	Neurological disease Age 5 y – 10 y	12 wk	Complete, Full
PK/PD	003	[5.4.3.2.3]	PK	Open-label, multicenter, dose-escalation, uncontrolled	MD Tolt PR qd PO for 12 wk 2 mg x 4 wk 4 mg x 4 wk 6 mg x 4 wk	11 safety 10 PK	Neurological disease Age 11 y – 15 y	12 wk	Complete, Full
Efficacy/Safety	020	[5.3.5.1.1]	Efficacy and Safety	Randomized, double-blind, multicenter, parallel-group, PBO-controlled	MD Tolt PR qd 2 mg PBO	235 107	≥1 incontinence or dampness episode/d Age 5 y – 10 y	12 wk	Complete, Full
Safety	021	[5.3.5.1.3]	Long term safety and tolerability	Open-label, multicenter, long-term extension uncontrolled	MD Tolt PR qd 2 mg 4 mg	278 20	Patients who completed study 018 or 020	12 mo	Complete, Full
Efficacy/Safety	008	[5.3.5.1.4]	Efficacy and Safety	Randomized double-blind, multicenter, parallel-group PBO-controlled	MD Tolt PR qd 2 mg PBO	252 117	≥1 incontinence or dampness episode/d ≥5 micturitions/d Age 5 y – 10 y	12 wk	Complete, Full

Abbreviations: BA = bioavailability, bid = twice daily, IR = immediate release, MD = multiple dose, m = month, OS = oral solution, PBO = placebo, PD = pharmacodynamics, PK = pharmacokinetics, PO = by mouth, PR = prolonged release, qd = once daily, SD = single dose, tolt = tolterodine

Source: Table 5.1, *5.2. pp 2-3*

4.3 Review Strategy

4.3.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- NDA 21-228 SE-8 Supplement No. 006; Submission Date of October 10, 2003
- NDA 21-228 Y-003; Submission Date of February 3, 2004

- NDA 21-228 SE-8 Supplement No. 006 supplement; Submission Date of February 13, 2004
- Written Request Letter dated January 23, 2001 and subsequent amendments
- Minutes of all regulatory meetings and telephone conferences with Sponsor that were contained in Division files

4.3.2 Review Processes and Procedures

The clinical review was based on the medical officer's review of the material delineated above and supplemented by the reviews conducted by Clinical Pharmacology and Statistics. Consults were also obtained from the Divisions of Drug Marketing, Advertising and Communication and the Office of Drug Safety.

4.3.3 Materials Reviewed

The review conducted by this medical officer focused on the ten studies and the report containing the two requested critical analyses submitted on October 10, 2003. All materials submitted on October 10, 2003, in electronic format for these studies and the report containing the two requested critical analyses were considered during the conduct of this review. Review focused on pharmacokinetic and pharmacodynamic data supporting pediatric labeling recommendations and safety issues, including drug-related serious adverse events, adverse events leading to patient withdrawal from the clinical trial, deaths, and adverse events. Additionally, safety update material submitted on February 3 and 13, 2004, was reviewed.

4.4 Data Quality and Integrity

4.4.1 DSI audits.

No site inspections were requested.

4.4.2 Central Laboratory

In Studies 001, 002, and 003, serum concentrations of tolterodine and DD01 were determined by using a LC/MS/MS assay. Determination of serum AGP was performed by . Genotyping was done by . Clinical laboratory and urinalysis tests were performed by local laboratories at each site. ECGs were read by . Urodynamic tracings were interpreted by local investigators and reviewed centrally by .

In Studies 020 and 008, serum concentrations of tolterodine and DD01 were determined by using a LC/MS/MS assay. In Study 020, genotyping was performed by . Determination of serum AGP was performed by . Clinical laboratory tests were performed by . Urinalyses were performed by local laboratories. ECGs were read by . Laboratory tests (other than dipstick urinalyses) were not conducted in Study 008 and ECGs were not conducted in Study 008 or 021.

Medical Officer's Comment:

Study 008 does not specify where genotyping and serum AGP analyses were performed.

4.4.3 Site Monitoring

In Studies 001, 002, and 003, data quality assurance was performed by Pharmacia & Upjohn by site audits and regular contact between investigators and the clinical study monitor. Statistical analysis was conducted by . In Studies 020, 008 and 021, study monitoring was

conducted by Pharmacia Market Companies. Four audits were conducted as part of the GCP compliance program in Study 020, eight sites were audited in Study 008 and two sites in Study 021.

4.5 Compliance with Good Clinical Practices

Protocol violations, including missing outcome data, constituted an important issue in both of the randomized placebo-controlled trials. Major protocol violations occurred in 27% of the tolterodine treated subjects in Studies 020 and 008. In 13% of tolterodine treated subjects in these two trials, the micturition diary (the source of the primary efficacy endpoint) was missing or invalid.

In addition, interpretation of the two randomized clinical trials was compromised by the use of a method of administration (opening the tolterodine capsule and sprinkling the beads on applesauce) for which bioequivalence with the intact capsule failed to be demonstrated and by the lack of identification of those subjects using that method of administration (in Study 020) and the absence of data examining the effect of method of administration on efficacy (in both studies).

4.6 Financial Disclosure

The sponsor submitted financial disclosure statements for Investigators who participated in five tolterodine efficacy trials (Studies 001, 002, 003, 008 and 020). This information was reviewed as part of the clinical review, and it was concluded that for four of the five studies:

- the information was complete
- appropriate documentation was received
- the information complied with 21 CFR 54
- no disclosable information was reported
- no conflicts of interests were noted
- there was no disclosure of financial interests that could bias the outcome of the trials

In Study 020, eight investigators in the U.K. are not listed as having provided disclosure documents; all other U.K. investigators and all investigators in the nine other countries participating in this trial submitted adequate documentation as above.

5 CLINICAL PHARMACOLOGY

Seven studies evaluated PK in children. Five of these (044, 018, 001-003) were intended primarily as PK studies, Studies 020 and 008 were randomized, placebo-controlled efficacy and safety trials that also included sparse PK sampling.

Studies 044, 018, 008, and 020 assessed children ranging in age from 5-15 years, with symptoms of urgency, frequency and urge incontinence. Studies 001-003 evaluated children with neurogenic lower urinary tract dysfunction, ranging in age from 3 months to 15 years. The children under age 11 received a tolterodine oral solution, which was not shown to be bioequivalent to Detrol tablets in a trial in healthy adults. Pharmacodynamics were assessed in all seven trials; in all studies except 020 and 008, the clinical efficacy variables were secondary endpoints. Symptom-based outcomes were evaluated in all trials; Studies 001-003 also used urodynamic endpoints. Finally, a population PK/PD analysis was performed using pooled data from Studies 020 and 008.

5.1 Pharmacokinetics

5.1.1 Relative Bioavailability

Two studies, which were not submitted in response to the Written Request, were conducted to assess the bioavailability of the two alternate formulations studied in these trials.

5.1.1.1 Study 004

Study 004 evaluated the relative bioavailability of beads from opened tolterodine prolonged release capsules with the intact capsules in 30 healthy adult volunteers. Subjects were dosed with 4 mg in one formulation on a single day, then crossed over to a single 4 mg dose of the alternate formulation after a 7 day washout period. Table 2 presents the data developed in this study.

Table 2 Bioavailability Confidence Intervals of Tolterodine, DD 01 and Active Moiety, Comparing Prolonged Release Beads to Intact Capsule

Analyte	Parameter	Tolterodine PR Beads Sprinkled over Applesauce vs Intact PR Capsule
Tolterodine	$AUC_{0-\infty}$	0.91 – 1.09
	Cmax	1.07 – 1.37
DD 01	$AUC_{0-\infty}$	0.97 – 1.06
	Cmax	1.12 – 1.35
Active moiety	$AUC_{0-\infty}$	1.03 – 1.14
	Cmax	1.21 – 1.43

* For statistical equivalence, the 90% confidence interval must fall between 0.800 and 1.25
These values represent the 90% confidence intervals around the ratio of the AUC or C_{max} for the beads over the respective value for the intact capsule (Log-transformed data)
Source: Table 6, *2.7.1, p 9*

The three moieties examined are the parent drug, the primary metabolite, which is pharmacologically active (DD 01), and the active moiety, defined as the sum of unbound tolterodine and DD 01. Bioequivalence was demonstrated for all three moieties on AUC, but was not demonstrated for any of the three on C_{max}. The beads had a 21% higher C_{max} for tolterodine than the intact capsule.

5.1.1.2 Study 005

Study 005 evaluated the relative bioavailability of tolterodine immediate release and two formulations of tolterodine oral syrup in 24 healthy adult volunteers. Subjects completed a randomized, three-way cross-over protocol, whereby they received a single 4 mg dose, either as 20 ml of 0.2mg/ml oral solution (one formulation characterized as "intended for commercial use" and one characterized as "prototype") or as two 2 mg tablets, followed by single doses of the two alternate formulations following a seven-day washout period between each dose. Table 3 displays the relative bioavailability of these three products. The flavored ("prototype") formulation was the one used in Studies 001 and 002.

Table 3 Bioavailability Confidence Intervals of Tolterodine, DD 01 and Active Moiety, Comparing Immediate Release Tablet to Two Oral Solution Formulations

Analyte	Parameter	Flavored/Colored Oral Solution vs IR Tablet	Flavored Oral Solution vs IR Tablet
Tolterodine	AUC0-∞	1.08 – 1.40	1.05 – 1.36
	Cmax	1.10 – 1.55	0.978 – 1.38
DD 01	AUC0-∞	1.00 – 1.14	0.980 – 1.11
	Cmax	0.986 – 1.20	0.890 – 1.09
Active moiety	AUC0-∞	1.00 – 1.09	0.974 – 1.06
	Cmax	0.982 – 1.18	0.878 – 1.05

For statistical equivalence, the 90% confidence interval must fall between 0.800 and 1.25
These values represent the 90% confidence intervals around the ratio of the AUC or C_{max} for the beads over the respective value for the intact capsule (Log-transformed data)
Source: Table 4, *2.7.1, p 8*

Bioequivalence was demonstrated for DD 01 and the active moiety on both AUC and C_{max}; it was not demonstrated for tolterodine itself. The "commercial" formulation had a 23% higher $AUC_{0\text{-infinity}}$ and a 30% higher C_{max} for tolterodine than the tablet; the "prototype" formulation had a 19% higher $AUC_{0\text{-infinity}}$ and a 16% higher C_{max} than the tablet.

5.1.2 *Pharmacokinetics in* Children

Two additional studies, which were also not in response to the Written Request, evaluated the pharmacokinetics (PK) of tolterodine in children.

5.1.2.1 Study 018

Study 018 enrolled 31 subjects aged 11-15 years with urinary urge incontinence, as manifested by urinary urgency (>= 8 micturitions/24 hours) and/or urge incontinence (at least one episode/week). The first ten subjects enrolled received a dose of 2 mg of prolonged-release tolterodine; following a safety review, the next 21 subjects received a 4 mg daily dose. Subjects were dosed for seven days (range 6-10 days), with the PK visit occurring on day 7 or 8. As the objective of this study was data collection to provide a basis for a dosage recommendation for children aged 11-15, the primary endpoint was $AUC_{0\text{-}24}$ for the active moiety, with secondary endpoints being PK parameters for the active moiety, tolterodine and DD 01, efficacy variables based on a micturition diary and safety variables including laboratory and ECG data, residual urine volume and adverse events.

Blood sampling for determination of the PK data was conducted pre-dose, and at 0.5, 1-4, 6, 9, 12, 24 and 25 hours post-dose on the PK day. Two subjects were excluded from the PK analysis, one as a major protocol violator on exclusion criteria, and one whose serum concentrations of tolterodine and DD 01 were all zero. Table 4, Table 5 and Table 6 present the PK data on tolterodine, DD 01 and the active moiety, respectively.

Table 4 PK Variables for Tolterodine

		Treatment		
		2-mg dose		4-mg dose
Variable		Extensive Metabolizer N=7	Poor Metabolizer N=2	Extensive Metabolizer N=20
AUC0-24 (µg·h/L)	Mean (SD)	39.4 (37.5)	210.5 (18.6)	42.8 (34.2)
	Median (min-max)	25.6 (2.5 - 108.5)	210.5 (197.3 - 223.7)	31.0 (8.7 - 123.8)
Cmax (µg/L)	Mean (SD)	3.22 (2.94)	10.76 (2.74)	3.43 (2.60)
	Median (min-max)	1.91 (0.35 - 8.34)	10.76 (8.82 - 12.70)	2.58 (0.56 - 9.87)
Tmax (h)	Mean (SD)	3.57 (1.28)	3.51 (0.72)	3.85 (1.57)
	Median (min-max)	3.00 (1.98 - 6.00)	3.51 (3.00 - 4.02)	3.53 (1.95 - 6.97)
t½ (h)	Mean (SD)	13.6 (4.5)	165.6 (161.4)	16.6 (13.4)
	Median (min-max)	14.2 (5.4 - 17.7)	165.6 (51.5 - 279.8)	9.9 (5.8 - 52.7)
Vss/F (L)	Mean (SD)	1204 (1366)	145 (26)	1492 (1223)
	Median (min-max)	637 (195 - 4031)	145 (127 - 163)	922 (224 - 4304)
CL/F (L/h)	Mean (SD)	103.6 (185.0)	1.06 (0.92)	81.2 (66.6)
	Median (min-max)	39.5 (7.9 - 520.1)	1.06 (0.40 - 1.71)	65.3 (10.9 - 234.7)

Source: Table 9.3.1.3.1, *5.3.3.2.1, p 48*

Table 5 PK Variables for DD 01

		Treatment	
		2-mg dose	4-mg dose
Variable		Extensive Metabolizer N=7	Extensive Metabolizer N=20
AUC0-24 (µg·h/L)	Mean (SD)	20.6 (9.2)	32.9 (11.6)
	Median (min-max)	18.5 (7.2 - 34.4)	31.0 (18.5 - 54.1)
Cmax (µg/L)	Mean (SD)	1.33 (0.56)	2.38 (1.01)
	Median (min-max)	1.26 (0.71 - 2.43)	2.38 (1.04 - 5.44)
Tmax (h)	Mean (SD)	4.71 (1.25)	5.00 (2.02)
	Median (min-max)	4.00 (3.00 - 6.00)	5.05 (1.97 - 9.00)
t½ (h)	Mean (SD)	14.8 (3.2)	15.3 (11.5)
	Median (min-max)	13.6 (11.6 - 19.6)	13.0 (6.4 - 51.4)

Source: Table 9.3.1.3.2, *5.3.3.2.1, p 49*

Table 6 PK Variables for Active Moiety

Variable		Treatment: 2-mg dose: Extensive Metabolizer N=7	2-mg dose: Poor Metabolizer N=2	2-mg dose: All N=9	4-mg dose: Extensive Metabolizer N=20
AUC0-24 (nM·h)	Mean (SD)	17.3 (6.0)	12.3 (0.2)	16.2 (5.6)	29.7 (11.1)
	Median (min-max)	17.4 (7.5 - 24.7)	12.3 (12.2 - 12.5)	16.2 (7.5 – 27.7)	26.7 (14.4 -52.3)
Cmax (nM)	Mean (SD)	1.23 (0.33)	0.62 (0.09)	1.10 (0.39)	2.17 (0.95)
	Median (min-max)	1.34 (0.75 - 1.57)	0.62 (0.56 - 0.69)	1.19 (0.56 – 1.57)	2.07 (0.93 - 5.25)

Source: Table 9.3.1.3.3, *5.3.3.2.1, p 49*

There was no apparent relation of AUC and C_{max} of the active moiety with subjects' age, and a negative association with body weight and BMI. It appears that a two-fold dose increase from 2 to 4 mg daily results in approximately a two-fold increase in AUC and C_{max} for the active moiety, whether extensive metabolizers or all subjects are considered. Comparison of PK data on the active moiety from this study with that obtained in adults and in younger children (Study 044) is shown in Table 7. Data for subjects receiving the 2 mg dose are normalized to a 4 mg dose (i.e., multiplied by 2).

Table 7 AUC and C_{max} of Active Moiety in Children and Adults

Variable		PR capsule: Children[1] *4 mg N=29	PR capsule: Adults[2] 4 mg N=17	IR tablet: Adults[3] *4 mg N=183	IR tablet: Children[4] 2 mg b.i.d. N=10
AUC0-24 (nM·h)	Mean (SD)	30.50 (11.00)	30.4 (13.7)	24.7 (8.8)	‡30.9 (9.7)
Cmax (nM)	Mean (SD)	2.18 (0.89)	2.3 (1.0)	-	7.6 (3.0)

[1] Study 018 [2] Study CTN 98-TOCR-006 [3] Based on summarized results of 14 studies in healthy volunteers [4] Study 044
* Normalized to 4 mg daily
Source: Table 10.1, *5.3.3.2.1, p 58*

Dosing of adolescents with 4 mg daily of prolonged release tolterodine appears to result in equivalent exposure (AUC and C_{max} for the active moiety) to that described in adults receiving the same dose.

5.1.2.2 Study 044

Study 044 was initiated prior to the Written Request, with the intent of extending the indication of tolterodine to include use in children. The trial enrolled 33 subjects aged 5-10 years with urinary urgency, frequency and/or urge incontinence, as manifested by urinary urgency (>= 8 micturitions/24 hours) and/or urge incontinence (at least one episode/week). The objective of this study was to evaluate the safety of 0.5, 1, 2 and 3 mg BID doses of tolterodine immediate release over a 14-day treatment period. The first eleven subjects enrolled received a dose of 0.5 mg of immediate-release tolterodine; following a safety review, the next 10 subjects were to receive the 1 mg dose, with this

sequential procedure continuing up to the 3 mg dose. However, plans for the 3 mg dose were discontinued after the AUC at the 1 mg BID dose exceeded the pre-specified threshold of 12 nmol*h/L (selected to equate with the exposure in adults receiving 4 mg BID). Subjects were dosed for 14 days, with the PK visit occurring on day 14. The primary endpoint, for safety, was the residual urine volume. Secondary objectives were to study the PK, tolerability and efficacy of these doses, with secondary endpoints being PK parameters for the active moiety, tolterodine and DD 01, efficacy variables based on a micturition diary and safety variables including laboratory and ECG data, and adverse events.

Blood sampling for determination of the PK data was conducted pre-dose, and at 0.5, 1-4, 6, and 8 hours post-dose on the PK day. Three subjects were excluded from the PK analysis, two who withdrew prior to the PK day due to adverse events, and one in whom blood sampling was unsuccessful. Table 8 and Table 9 present the C_{max} and AUC, respectively, for tolterodine and DD 01; Table 10 shows these data for the active moiety.

Table 8 C_{max} for Tolterodine and Metabolites

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	3.4 ± 3.0	4.9 ± 2.9	11.5 ± 6.5
	n = 9[a]	n = 10	n = 9[b]
DD 01	2.0 ± 0.9	4.6 ± 1.7	8.5 ± 4.0
	n = 9	n = 10	n = 9
Dealkylated hydroxylated tolterodine	0.3 ± 0.1	0.7 ± 0.3	1.8 ± 0.9
	n = 6	n = 9	n = 9
Tolterodine acid	3.6 ± 1.7	7.5 ± 2.9	13.0 ± 4.9
	n = 9	n = 10	n = 9
Dealkylated tolterodine acid	1.9 ± 0.8	3.3 ± 0.8	6.6 ± 2.3
	n = 9	n = 10	n = 10[c]

PM patients: [a]No. 9 Cmax = 6.8; [b] No. 29 Cmax = 41.6; [c]No. 29 Cmax = 0.3

Source: Table 10.3.4.1.2, *5.3.3.2.3, p 51*

Table 9 AUC for Tolterodine and Metabolites

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	11.2 ± 13.5	14.8 ± 10.2	31.7 ± 16.3
	n = 9[a]	n = 10	n = 9[b]
DD 01	7.6 ± 2.5	17.4 ± 8.3	34.1 ± 12.0
	n = 9	n = 10	n = 9
Dealkylated hydroxylated tolterodine	‡	3.1 ± 0.6	8.7 ± 3.5
	n = 2	n = 8	n = 9
Tolterodine acid	20.7 ± 4.9	39.4 ± 8.9	77.1 ± 25.3
	n = 9	n = 10	n = 9
Dealkylated tolterodine acid	12.0 ± 4.2	21.0 ± 3.1	48.2 ± 12.5
	n = 9	n = 10	n = 8

‡ 2.6 and 2.8 µg·h /L

PM patients: [a]No. 9 AUC = 61; [b]No. 29 AUC = 211;

Source: Table 10.3.4.1.3, *5.3.3.2.3, p 51*

Table 10 PK Variables for Active Moiety

	0.5 mg bid	1 mg bid	2 mg bid
Cmax (nM)	1.8 ± 0.8	3.9 ± 1.4	7.6 ± 3.0
AUC (nM ·h)	7.2 ± 2.4	13.9 ± 4.9	30.9 ± 9.7

Includes EM and PM, N=10 in each group

Source: Table 10.3.3.2.1, *5.3.3.2.3, p 53*

There does not appear to be dose-linearity for increasing doses of tolterodine and DD 01; however, the C_{max} and AUC of the active moiety do increase in a linear fashion with doubling doses. Comparison of PK data on the active moiety from this study with that obtained in adults is shown in Table 11.

Table 11 AUC and C_{max} of Active Moiety in Children and Adults

Parameter	Children, 1 mg bid (n=10)	Adults[1], 2 mg bid (n=24)	Adults[2], 2 mg bid (n=18)
Cmax (nM)	3.9 ± 1.4	3.4 ± 1.7	2.8 ± 0.82
AUC (nM·h)	14 ± 4.9	14 ± 6.4	15 ± 4.3

Source: Table 11.1, *5.3.3.2.3, p 62*

Dosing of children aged 5-10 with 1 mg BID of immediate release tolterodine appears to result in equivalent AUC and C_{max} for the active moiety to that described in adults receiving 2 mg BID.

5.1.2.3 Studies in Neurogenic Bladder

In Studies 001 and 002, subjects were dosed by weight, with the PK dose being 0.03 mg/kg BID, or 0.06 mg/kg/day. In Study 001, the mean daily dose at this dose level was 0.71 mg/day. Active moiety exposure at this dose in these children, aged 3 months to 4 years, was similar to that seen in Study 044 (5-10 year olds) who received 1 mg daily, and was about half that seen in adults taking 2 mg BID (see Table 21) No clear dose- or exposure-response relationships were demonstrable. In Study 002, with children aged 5-10 years, the mean daily dose at the PK dose level was 1.7 mg/day. Data were very similar to that seen in Study 044 in children of the same age who received 1 mg daily of the IR tablets, and again, exposure was about half that seen in adults taking 2 mg BID (see Table 35). Again, no clear dose- or exposure-response relationships with clinical effect variables were shown. Study 003, conducted in children aged 11-15 years, no longer used weight-based dosing. The PK dose was 4 mg/day of the prolonged release capsule (or the beads sprinkled on applesauce – a formulation also not found to be bioequivalent to Detrol LA). PK results in this population were very similar to those seen in Study 018 and in adults receiving the 4 mg daily dose (see Table 48). Again, there were no dose- or exposure-response effects in this population.

5.1.2.4 Studies in Urinary urge incontinence

A population pharmacostatistical model was constructed using the data from Studies 044 and 018; this model was then tested on pooled data from Studies 044, 018, 020 and 008. The initial model showed that a three-compartment model best described the PK of tolterodine – with compartments for drug depot, tolterodine and DD 01. Significant covariates in the final model were formulation/age (which were confounded), metabolic phenotype, alpha-1-acid glycoprotein concentration, body size, race and presence of a concomitant CYP3A4 inhibitor. This model was then used to estimate drug exposure in the subjects in Studies 020 and 008.

In Study 008, PK data were available on 220 or 87% of the subjects receiving tolterodine. In Study 020, only 102, or 43%, of the tolterodine-treated subjects provided PK data. The steady state AUC_{0-24} of the active moiety was 20.9 nM*h and 20.5 nM*h in Studies 008 and 020, respectively. This was about 31% lower than the exposure seen in adults receiving double the dose of tolterodine prolonged release daily – which, based on Study 018, was expected to approximate the exposure 5-10 year olds achieved on half the adult dose.

Medical Reviewer's Comment:

> **No explanation is provided for the discrepancy between the findings of Study 018 and the pooled PK data from Studies 020 and 008. Although the method of dosing may have differed between the studies (020 and 008 allowed use of sprinkled beads from opened capsules), the bioequivalence data do not suggest a pronounced decrease in exposure with use of the beads.**

5.2 Pharmacodynamics and Exposure- Response Relationships

No exposure-response relationships were demonstrable in the three small studies in children with neurogenic lower urinary tract dysfunction.

In order to explore possible exposure-clinical response relationships in the randomized, placebo-controlled trials, statistical models were constructed by the sponsor based on the data from Study 008 to determine breakpoints in the AUC_{0-24} of the active moiety associated with statistically significant change from baseline in the number of daytime incontinence episodes as compared to placebo. A Classification and Regression Tree (CART) procedure identified threshold active moiety AUC_{0-24} values of 14.4 nM*h in Study 008 and 12.6 nM*h in Study 020 to be significantly associated with

improvement in incontinence. Although these threshold levels are below the mean AUC_{0-24} values seen in the two studies, a substantial proportion of the tolterodine-treated subjects in each study failed to achieve these threshold exposures. Depending on the weight group evaluated, as many as 40-67% of the heavier subjects in Study 008 were apparently under-dosed. Multiple linear regression showed threshold AUC value and baseline frequency of incontinence as the only significant predictors of efficacy.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Neurogenic Lower Urinary Tract Dysfunction

6.1.1 Methods

The three studies for this indication, Studies 001, 002 and 003 were uncontrolled, open label, dose escalation trials evaluating three doses of tolterodine in patients with neurogenic lower urinary tract dysfunction. Studies 001 and 002, in children aged 3 months – 4 years and 5-10 years, respectively, used an oral formulation of tolterodine, which is not commercially available, and dosed subjects by weight on a BID schedule. Study 003, in children aged 11-15 years, used escalating, non-weight-based doses of the prolonged release tolterodine capsule, which is dosed daily.

6.1.2 General Discussion of Endpoints

No efficacy endpoint was designated as primary in Studies 001, 002 or 003, as the primary objective was pharmacokinetic in nature. Clinical effect endpoints in these studies included both data obtained by urodynamic evaluation and data derived from patient diaries. The urodynamic variables were:

- volume to first detrusor contraction of >10 cm H_2O pressure ,
- functional bladder capacity and leak point pressure,
- intravesical volume at 20 and 30 cm H_2O pressure,
- maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure),
- bladder compliance at 0-20, 0-30 and 0-40 ml/cm H_2O and
- percent change in cystometric capacity

Some of the urodynamic variables (maximal cystometric capacity and bladder wall compliance) were unable to be obtained for all subjects due to patient discomfort during the procedure.

Dose-pharmacodynamic (PD) effects for tolterodine were determined by assessing the urodynamic parameters at each of the three dose levels; concentration-PD effects for the active moiety were determined by assessing the urodynamic parameters at the pharmacokinetic (PK) dose (0.06 mg/kg/day for Studies 001 and 002; 4 mg/day for Study 003). The urodynamic variables were characterized by descriptive statistics, change from baseline and percent change from baseline at weeks 4, 8 and 12.

The patient diary variables were:

- mean number of catheterizations or micturitions per 24 hours,
- mean volume per catheterization/micturition and
- mean number of incontinence episodes per 24 hours, with the incontinence episodes further classified as to severity on a four point scale

and were based on means derived from three-day diary recordings done at baseline and at each dose period (weeks 4, 8 and 12).

The variables most likely to have clinical relevance are volume to first detrusor contraction, intravesical volume at 40 cm H_2O and bladder compliance at 0-40 ml/cm H_2O, as well as the patient diary variable number of daily incontinence episodes.

Pharmacokinetic endpoints in Study 001and 002 were the serum PK of the active moiety, including AUC_{0-12}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12}, F_{ext}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints. Study 003 evaluated the same parameters, differing only in that the AUC period was 0-24 hours rather than 0-12 hours, and the F_{ext} was not measured.

6.1.3 Efficacy Findings: Studies in Neurogenic Lower Urinary Tract Dysfunction

The sponsor did not conduct hypothesis testing in these three studies; thus, no p-values were provided in the study reports. The statistical reviewer conducted significance testing of the change from baseline and test of trend for a dose-response effect, from which the p-values described below are derived. The values described below are based on the mean values at each dose period.

In Study 001, volume to first detrusor contraction was significantly higher at dose 3 (56.9 ml) than at baseline (21.7ml). There was also a significant dose-response trend (p=0.006). Similarly, number of incontinence episodes were significantly fewer at dose 2 (4.4) and dose 3 (4.0) than at baseline (5.2), with a significant dose-response trend (p=0.02), and volume/micturition increased significantly from baseline (34.9 ml) to dose 2 (40.6 ml) and to dose 3 (55.1 ml), with a significant dose-response trend (p=0.018). Intravesical volume at 20 cm H_20 and bladder wall compliance from 0-20 ml/cm H_2O also showed significant increases at doses 2 and 3, with statistically significant dose-response trends, but the clinical relevance of these results is uncertain. The remaining variables either showed significant improvement at dose 2 (functional bladder capacity, leak point pressure) only, or were not significantly different from baseline. In exploration of the exposure-effect relationship, there was no correlation between AUC_{0-12} of the active moiety and change from baseline in either volume to first detrusor contraction or functional bladder capacity. There was also no relationship between AUC_{0-12} of the active moiety and change from baseline in any of the diary variables.

Similarly, in Study 002, volume to first detrusor contraction increased significantly from baseline (38.4 ml) at all three dose levels (57.7 ml, 63.3 ml and 65.1 ml, respectively). However, the dose-response trend was not statistically significant. The number of incontinence episodes also decreased significantly from baseline (4.3) at each dose level (3.7, 3.2 and 3.1, respectively), and the dose-response trend was significant (p=0.02). The remaining variables were either significantly different from baseline at one or two of the three dose levels, or were completely non-significant, and none showed a significant dose-response trend. Again, there was no relationship between AUC_{0-12} of the active moiety and change from baseline in the urodynamic variables. There was no relationship between AUC_{0-12} of the active moiety and change from baseline in any of the diary variables.

Study 003 differed from Studies 001 and 002 in that the patients received tolterodine extended release capsules and were not dosed by body weight. None of the variables displayed a statistically significant dose-response trend. Statistically significant difference from baseline was demonstrated only for the number of incontinence episodes, at all doses (baseline – 2.4, dose 1 – 1.7, dose 2 – 1.4, dose 3 – 1.5) and for functional bladder capacity where dose 1 (311.1 ml) and dose 3 (286.1 ml) were significantly greater than baseline (232 ml). Interpretation of data on the intravesical volume and bladder wall compliance variables is hampered by very small sample sizes. There was no relationship between AUC_{0-12} of the active moiety and change from baseline in any of urodynamic or the diary variables.

Medical Reviewer's Comment:

The lack of consistent effects across the three studies, the general lack of dose-response trends and the lack of a placebo control leads this reviewer to conclude that efficacy of tolterodine in a pediatric population suffering from urinary incontinence related to neurogenic lower urinary tract dysfunction has not been demonstrated.

6.2 Indication: Urinary urge incontinence

6.2.1 Methods

The two primary studies are large, 12-week duration, randomized, double-blind, placebo-controlled trials evaluating a single dose of tolterodine prolonged release capsule on a variety of clinical efficacy variables. A twelve-month extension trial followed Study 020 and enrolled almost 80% of participants.

6.2.2 General Discussion of Endpoints

The primary efficacy endpoint in both Studies 020 and 008 was change from baseline to week 12 in the number of daytime incontinence episodes per week. Secondary efficacy endpoints included change from baseline in:

- Number of "gross" incontinence episodes after 12 weeks of treatment (Study 020)
- Number of weekly incontinence episodes after four weeks of treatment (Study 008)
- Mean number of daily micturitions after 12 weeks (both studies; also after four weeks in Study 008)
- Mean urinary volume per micturition after 12 weeks (both studies; also after four weeks in Study 008)
- Number of nights with nocturnal enuresis after 12 weeks (both studies; also after four weeks in Study 008)
- Number of dry days per week (Study 020)
- Proportion of subjects continent by week 12 (both studies; also after four weeks in Study 008)
- Visual Analog Scale for Children (VASC) (Study 020)
- Parental assessment of treatment benefit (Study 020)
- Pediatric Enuresis Module to Assess the Quality of Life (PEMQoL)
- Treatment Satisfaction Questionnaire (Study 008)

6.2.3 Efficacy Findings

Neither Study 020 nor 008 demonstrated a statistically significant change in the number of weekly incontinence episodes after 12 weeks of treatment. In Study 020, the tolterodine group showed a decrease from 14.2 episodes/week to 8.9 episodes/week, a reduction greater than that seen in placebo subjects by 1.5 weekly episodes (p=0.07). In Study 008, the tolterodine group decreased from 19.4 to 9.3 weekly episodes, a reduction that was only 1.2 episodes per week greater than that seen in placebo subjects (p=0.4).

Excluding exploratory subgroup analyses, the only statistically significant findings in Study 020 were:

- a greater increase in volume per micturition (tolterodine subjects increased from a baseline value of 98.7 ml/void to 112.4 ml, or 7.9 ml per micturition greater than the change seen in placebo subjects, p=0.03) and
- a 15% higher perception of treatment benefit among parents of those children treated with tolterodine as compared to placebo (p=0.01).

In Study 008, there was similarly a statistically significantly greater increase in volume per micturition as compared to baseline in the tolterodine group at both four and twelve weeks, from a baseline of 85.3 ml/void to 98.6 ml at week 4 and 104.8 ml at week 12. These improvements were, respectively, 6.6 ml/void and 9.1 ml/void greater than those seen in placebo subjects (p=0.047 at four weeks, p=0.02 at 12 weeks). There were also significantly greater improvements in three of ten questions in the Treatment Satisfaction Questionnaire (quality of life, improvement in symptoms and satisfaction with outcome); however, these statistics were not adjusted for multiple comparisons.

Medical Reviewer's Comment:

The sponsor did not report results from the ITT population for the secondary efficacy variable volume per micturition in Study 020. The statistically significant result reported is based upon the Statistics reviewer's analysis of the sponsor's data.

6.3 Efficacy Conclusions

The reviewer concludes that efficacy of tolterodine in a neurologically normal pediatric population with urinary urgency, frequency and urge incontinence has not been demonstrated. This conclusion is based on the fact that neither study demonstrated statistically significant improvement from baseline as compared to placebo in the primary efficacy endpoint, and that the only secondary endpoints with statistically significant change (small increase in volume per micturition, some degree to greater parental satisfaction with treatment) are of doubtful clinical significance.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data from eight submitted trials (excluding the two small bioavailability studies conducted in adult volunteers) were reviewed. Additional information submitted by the sponsor included the 2003 Annual Report and final study reports of Study 007 and 009, which were ongoing at the time of the full submission. Study 007 was a 6 month, open-label, uncontrolled safety and efficacy study of tolterodine immediate release solution in children aged 5-10 years with urinary urgency, frequency and urge incontinence. Study 009 was a 12-month safety extension study to Study 008. Table 12 summarizes adverse event findings from all ten trials conducted in children.

Table 12 Summary of Adverse Event Data per Subject

Study	001	002	003	020 Tolt	020 Placebo	008 Tolt	008 Placebo	021*	018	044	007	009*
Age Gp	0-4	5-10	11-15	5-10	5-10	5-10	5-10	5-15	11-15	5-10	5-10	5-11
Formul	IR syrup	IR syrup	PR capsule	PR cap-sule	PR capsule	PR cap-sule	PR capsule	PR cap-sule	PR cap-sule	IR tablet	IR syrup	PR cap-sule
Duration	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks	12 mos	6-10 days	14 days	6 mos	12 mos
Deaths	0	0	0	0	0	0	0	0	0	0	0	0
SAEs**	2	0	2	4	2	3	0	8	0	0	1	4
Withdrawn	1	0	0	11	5	4	2	8	0	2	3	10
UTI/cystitis	4	7	4	11	3	19	6	24	0	0	37	27
Pyelo	0	0	0	2	1	0	0	2	0	0	2	***
All Psych	0	0	0	14	1	7	5	9	1	1	7	17
Aggressive & Abnl Behavior	0	0	0	5	0	4	1	5	0	0	1	3
Activity/ Attention Disorder	0	0	0	3	1	2	0	2	0	0	6	6
Seizures	1	0	0	0	0	0	0	0	0	0	1	1
Total N exposed	19	15	11	235	107	251	117	298	31	33	142	318

*12-month safety extension studies
** All counts are per subject except SAEs, which are total counts (26 events occurred in 22 subjects)
***Specific infections are listed only if they exceeded 1% of the population; thus it is not possible to determine if fewer than 1% developed pyelonephritis

7.1.1 Deaths

There were no deaths in any of the trials.

7.1.2 Other Serious Adverse Events

In the ten pediatric studies submitted, there were a total of 26 serious adverse events (SAEs), 12 of which occurred in the two 12-month extension studies (021 and 009). Only two of the trials contained a placebo group, and only two placebo subjects experienced an SAE. Only the two placebo subjects with SAEs were discontinued from the study due to the adverse event, and the only SAE considered by the sponsor to be treatment-related was a case of pyelonephritis in a placebo patient. SAEs and their frequency were:

- UTI – 4
- Pyelonephritis – 4 (1 placebo, 3 tolterodine subjects)
- Fever – 3 (2 occurred in subjects with a second SAE [1 pyelonephritis, 1 UTI], 1 associated with symptoms suggestive of pyelonephritis)
- Fracture – 3 (1 placebo subject – femur, 2 tolterodine subjects – arm & femur)
- Procedure site reaction
- Erythema
- Pressure sores (same subject who experienced erythema)
- Reduced visual acuity

- Head injury
- Abscess behind R knee
- Lens implantation
- Lumbar puncture (indication not provided)
- Testicular torsion
- Pneumonia
- Appendicitis
- Epilepsy

Medical Reviewer's Comments:

1) **The sponsor's attribution of no relationship to tolterodine for the SAEs of pyelonephritis and UTI may be questioned. In Study 020, in which pyelonephritis occurred in one placebo subject and one tolterodine subject, treatment-relatedness was attributed to the placebo case but not to the tolterodine case, for reasons that are not explained. For five subjects with an upper or lower urinary tract infection in whom post void residual urine volumes (PVRs) were determined, none had a PVR elevated above 20% of theoretical bladder capacity. However, in the placebo-controlled trials, PVR did show a greater increase with tolterodine than with placebo, and it is possible that even small increases may predispose susceptible children to urinary tract infections.**
2) **The association of tolterodine with new onset or exacerbations of seizure disorders in three studies and the AERS database, along with the association with CNS stimulation makes the sponsor's determination that the case of absence seizures included among the SAEs is not related to medication questionable.**
3) **The reviewer agrees with the sponsor that all other SAEs are unlikely to be related to tolterodine treatment.**

7.1.3 Dropouts and Other Significant Adverse Events

In the data pooled from the two placebo-controlled studies (020 and 008), the rate of withdrawal due to AEs was identical in the tolterodine and placebo groups, 3%. Over all studies, a total of 46 subjects (39 treated with tolterodine and 7 with placebo) withdrew due to adverse events. Events leading to withdrawal (numbers exceed 46 because of multiple events occurring in some subjects) and their frequency were:

- Difficulty in micturition/PVR >= 20% theoretical bladder capacity: 9 (8 tolterodine, 1 placebo subjects)
- Mood alteration/aggression/abnormal behavior: 9 (in 6 tolterodine subjects)
- Abdominal pain: 4 tolterodine subjects
- UTI/pyelonephritis: 4 (3 tolterodine, 1 placebo subjects)
- Aggravated incontinence: 4 (3 tolterodine, 1 placebo subject)
- Headache: 3 tolterodine subjects
- Dermatitis/Blister/rash: 3 (2 tolterodine, 1 placebo subjects)
- Photophobia/Eye irritation: 3 (in 1 placebo subject)
- Fecal incontinence: 2 tolterodine subjects
- Micturition urgency/enuresis: 2 (in 1 placebo subject)

- Disturbance in attention: 1 tolterodine subject
- Tachycardia (HR 116): 1 tolterodine subject
- Disturbed accommodation: 1 tolterodine subject
- Increased weight: 1 tolterodine subject
- Decreased appetite: 1 tolterodine subject
- Elevation of AST: 1 tolterodine subject
- Nausea: 1 tolterodine subject
- Increased activity: 1 tolterodine subject
- Dry skin: 1 tolterodine subject
- Disturbance in attention: 1 tolterodine subject
- Constipation: 1 tolterodine subject
- Syncope: 1 tolterodine subject
- Diarrhea: 1 tolterodine subject
- Menstrual disorder: 1 tolterodine subject
- Fatigue: 1 placebo subject
- Femur fracture: 1 placebo subject

Medical Reviewer's Comment:

The Overview of Safety report incorrectly states that three tolterodine subjects withdrew from Study 008; in fact, four subjects in the treatment arm withdrew due to adverse events.

7.1.4 Other Search Strategies

A consult was performed by the Office of Drug Safety, which reviewed the safety information available concerning pediatric exposure to tolterodine in the AERS database (see Section 3.5). A Pubmed literature search was also conducted to identify any recent publications that would bear on safety of tolterodine in children. In addition to the five pediatric studies cited by the sponsor in the Critical Analysis, two additional pediatric publications were identified in the literature (Raes et al[1] and Nijman[2]).

An uncontrolled, retrospective records review by Raes et al evaluated 256 children with overactive bladder treated with tolterodine. Safety results showed no SAEs, three behavior disorders (including one case of aggression) and six gastrointestinal adverse events. Two subjects withdrew due to adverse events (not further specified). Nijman published a review of pediatric nonneurogenic urinary incontinence, including three of the studies cited by the sponsor.

7.1.5 Common Adverse Events

Table 13 shows the adverse events occurring with >= 1% incidence in the two randomized placebo-controlled trials. Events that occurred with at least twice the frequency in tolterodine vs. placebo-treated subjects were: Diarrhea NOS, Constipation, Ear infection NOS, Abnormal behavior NOS and Rhinitis NOS. The adverse events reported in Table 13 were seen with a dose of tolterodine which was not shown to be effective in this pediatric population.

Table 13 Most Common Adverse Events (>= 1%) in Placebo Controlled Trials

System Organ Class – Preferred Term (MedDRA)	Study 020 + Study 008	
	Tolterodine PR 2 mg QD N = 486	Placebo N = 224
	n (%)	n (%)
Gastrointestinal disorders	79 (16.3)	32 (14.3)
– Abdominal pain NOS	22 (4.5)	7 (3.1)
– Vomiting NOS	17 (3.5)	5 (2.2)
– Diarrhea NOS	16 (3.3)	2 (0.9)
– Abdominal pain upper	15 (3.1)	7 (3.1)
– Constipation	10 (2.1)	2 (0.9)
– Nausea	6 (1.2)	5 (2.2)
– Sore throat NOS	6 (1.2)	6 (2.7)
– Dry mouth	4 (0.8)	4 (1.8)
General disorders & administration site conditions	21 (4.3)	14 (6.3)
– Pyrexia	18 (3.7)	10 (4.5)
– Fatigue	3 (0.6)	4 (1.8)
Infections and infestations	60 (12.3)	28 (12.5)
– Urinary tract infection NOS	33 (6.8)	8 (3.6)
– Nasopharyngitis	18 (3.7)	11 (4.9)
– Ear infection NOS	5 (1.0)	1 (0.4)
– Upper respiratory tract infection NOS	5 (1.0)	5 (2.2)
– Influenza	3 (0.6)	5 (2.2)
Musculoskeletal, connective tissue, & bone disorders	2 (0.4)	3 (1.3)
Arthralgia	2 (0.4)	3 (1.3)
Nervous system disorders	36 (7.4)	18 (8.0)
Headache NOS	35 (7.2)	17 (7.6)
Dizziness (except vertigo)	3 (0.6)	3 (1.3)
Psychiatric disorders	8 (1.6)	1 (0.4)
Abnormal behavior NOS	8 (1.6)	1 (0.4)
Renal and urinary disorders	8 (1.6)	6 (2.7)
Difficulty in micturition	7 (1.4)	3 (1.3)
Urinary incontinence aggravated	1 (0.2)	3 (1.3)
Respiratory, thoracic, & mediastinal disorder	24 (4.9)	13 (5.8)
Cough	12 (2.5)	10 (4.5)
Rhinitis NOS	8 (1.6)	1 (0.4)
Epistaxis	5 (1.0)	2 (0.9)
Skin & subcutaneous tissue disorders	8 (1.6)	6 (2.7)
Dermatitis NOS	7 (1.4)	3 (1.3)
Eczema NOS	1 (0.2)	3 (1.3)

Source: Table 3, *2.5, p 27*

Although not quite occurring at twice the placebo rate, the elevated frequency of UTIs is notable. UTIs occurred in every study except the two conducted for only 1-2 weeks. Even acknowledging that the majority of UTIs in these studies occurred in females (as do UTIs in the general pediatric population) and that both neurogenic lower urinary tract dysfunction and urinary urgency, frequency and urge incontinence in children may predispose to UTI, the increase seen over placebo-treated subjects suggests that treatment with tolterodine may increase the risk of UTI. In general, tolterodine led to a minor increase in PVR; possibly this is sufficient to lead to UTI in susceptible children.

Medical Reviewer's Comment:

The numbers cited in Table 13, which is from the study report, do not concur precisely with counts obtained by the reviewer after evaluating the line listings for adverse events. For example, the sponsor coded "cystitis" separately from UTI and the two cases occurring in tolterodine treated subjects are not included in the table. In other cases, it appears that events were counted by the sponsor *in toto*, rather than per subject, leading to slightly higher counts than the reviewer obtained.

7.1.6 Less Common Adverse Events

Two classes of adverse events that occurred with relatively low frequency are of concern. These are aggressive/abnormal behavior and seizures.

A total of 18 subjects manifested aggressive and/or abnormal behavior while on tolterodine. Although behavioral problems may be associated with urinary incontinence, examination of the placebo-controlled trials allows evaluation of a homogeneous population, differing only in their exposure to tolterodine. In these trials, nine tolterodine-treated subjects experienced aggressive or abnormal behavior. By comparison, only one placebo subject experienced such behavior. In six tolterodine subjects, the behavior was marked enough to cause withdrawal from the trial. This may represent a paradoxical CNS stimulatory effect of the drug.

A 7 year old subject in Study 002 with a known seizure disorder experienced increased seizure frequency during dose periods 1 and 2, during which she was receiving 0.83 mg BID and 1.66 mg BID, respectively. The seizures in each instance occurred on a single day, occurring toward the end of the dosing period. A second subject, age 11, in Study 007 experienced exacerbation of a pre-existing seizure disorder after almost two months of treatment with 1 mg tolterodine BID. In Study 009, an 8 year old boy was seen by a neurologist and diagnosed with unspecified neurological problems prior to starting 2 mg daily of tolterodine. Absence seizures were first noted two to three months after beginning the drug. None of these events were judged to be related to tolterodine treatment by the sponsor. An additional child was noted in the AERS database to have onset of a seizure disorder at an unknown time after beginning tolterodine treatment. None of these episodes occurred in a placebo-controlled trial, so no comparison to the expected occurrence in the general population can be made. However, it does appear that tolterodine may be associated with CNS stimulatory effects in some children, and it is possible that this may lead to lowering of the seizure threshold in susceptible children.

7.1.7 Laboratory Findings

The majority of the studies reviewed included hematology, clinical chemistry and urinalysis as safety measures. Although generally changes in laboratory parameters were small and not of clinical significance, there were two cases of elevated liver function tests that may be significant. A 10-month old child in Study 001 was withdrawn from the trial after her AST rose from 61 IU/L at baseline to 111 IU/L at dose level 2 (she was receiving 0.26 mg BID at that time). The AST value declined almost to baseline in two weeks. An eight year old girl in Study 007 had an ALT of 161 IU/L at the end of treatment; however, this subject's baseline value was not determined.

Medical Reviewer's Comment:

Both of the cases of elevated transaminases are difficult to interpret. One subject had an elevated level at baseline and the other subject did not have a baseline measurement.

7.1.8 Vital Signs

In all studies, changes in vital signs were small and not judged to be clinically relevant.

7.1.9 Electrocardiograms (ECGs)

In Studies 001 and 002, ECGs were performed at screening, once every 15 minutes for one hour at Visits 2, 3 and 5, and coincident with each blood draw at Visit 4 (a total of 6 ECGs). The T_{max} was approximately one hour. In Study 001, mean uncorrected and corrected (Fridericia) QT intervals showed no significant change over dose periods. Both corrected and uncorrected QT intervals tended to decrease slightly at dose periods 1 and 2; mean values at dose period 3 were nearly identical to values at baseline. Using QTcF, one subject had an increase > 30 msec in dose period 1, three in dose period 2 and two at dose period 3. The maximum increase was 51 msec. In Study 002, mean corrected (Fridericia) and uncorrected QT intervals showed no significant change compared to baseline over the 3 dose periods. Using QTcF, two subjects had an increase of >30 msec at each dose period; the maximum was 43 msec.

In Study 003 (Detrol LA), subjects had ECGs monitored at intervals of 0, 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose at dose level 2 (4 mg/day) and two hours post-dose at dose levels 1 and 3 The T_{max} was approximately 3 hours. The mean QTcF decreased approximately 10 msec at all 3 dose levels. A single patient, 10% of the population, showed a > 30 msec increase in QTcF at the highest dose (maximum QTcF increase of 51 msec).

Medical Reviewer's Comment:

The lack of a placebo or positive control group do not allow definitive conclusions concerning QT data to be made.

In the randomized controlled trial 020, ECGs were performed from 3 to 9 hours after the final dose was administered. The placebo group had a greater frequency of QTcF increases > 30 msec than did the tolterodine group. ECGs were not performed in Study 008.

7.1.10 Withdrawal Phenomena/Abuse Potential

No abuse potential for this drug in the pediatric population is expected.

7.1.11 Overdose Experience

No clear overdose reports are found.

7.1.12 Post-marketing Experience

Spontaneous reports to the AERS database are described in Section 3.5 The sponsor included the Periodic Safety Update Report for the period 9/6/02 to 3/5/03. During this time period, as part of marketing renewal in several European countries, the sponsor proposed changing the label to include caution regarding use in patients with known risk factors for QT- prolongation, to add angioedema and cardiac failure as very rare adverse events and to add palpitations and arrhythmias as class effects. Only four cases in the Update report use in children; no deaths were reported in children.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent and Adequacy of Overall Clinical Experience

The pediatric trial database includes 1577 subjects, of whom 1353 were exposed to tolterodine. Only two of the trials, however, with a total of 710 subjects, were placebo-controlled, allowing for

comparison of adverse event rates. In these studies, it appears that dosing may have been inadequate to achieve exposure comparable to adults for a substantial proportion of subjects; thus, a higher dose of tolterodine, which the sponsor suggests may be necessary for efficacy, would not have adequate safety data available at this time.

7.2.2 Adequacy of Special Animal and/or In vitro Testing

No animal or in vitro data were submitted in this efficacy supplement.

7.2.3 Adequacy of Routine Clinical Testing

The sponsor evaluated appropriate laboratory parameters, and had ECG data from four studies (001-003, 020). In the three neurogenic studies, ECG sampling was done at various intervals after dosing – most commonly two hours post-dose. T_{max} of the drug ranged from one hour for the oral solution to over three hours for the prolonged release capsule. Thus, in the single study with prolonged release capsules, the assessment of ECG parameters occurred prior to maximum drug exposure and may represent an underestimate of tolterodine's cardiac effect. In Study 020, ECGs were obtained from 3-9 hours post-dose at the end of treatment. Estimating Tmax at 3-4 hours, ECGs at 5 or more hours post-dose may not be indicative of the full effect of the drug.

7.2.4 Adequacy of Metabolic Clearance and Interaction Workup

No pediatric studies relevant to metabolic clearance or interaction were submitted.

7.3 Safety Conclusions

Overall, tolterodine, at the doses administered, was shown to be generally safe and well tolerated in the pediatric population. No deaths occurred. Twenty-six serious adverse events occurred, but with the exception of eight cases of upper and lower urinary tract infections and one case of seizures, the reviewer agrees with the sponsor that these events are unlikely to be related to tolterodine. Three signals of concern were noted:

- Increased frequency of UTI in subjects exposed to tolterodine, which may be related to the increased postvoid residual volume seen in exposed subjects in several trials.
- Increased frequency of psychiatric/behavioral disorders, particularly aggressive behavior, seen in children treated with tolterodine. Such reports were noted both in the clinical trial data and in spontaneous case reports in the AERS database. Although data from the AERS database cannot be thought to describe incidence or prevalence of adverse effects, it is notable that about one-third of all reported pediatric cases related to behavioral disorders, a number of which showed a positive dechallenge response. These behavioral problems may represent a paradoxical CNS agitation reaction in children exposed to tolterodine.
- There are rare reports of initiation or exacerbation of seizures in children on tolterodine. While the treatment-relatedness of these reactions is difficult to assess, it is plausible that a CNS stimulatory effect might lower the seizure threshold and cause worsening of an existing seizure disorder or unmasking of a latent condition.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor acknowledges that efficacy has not been demonstrated for tolterodine in a pediatric population. No dosing regimen is recommended. The sponsor notes that, while children aged 11-15 appear to have equivalent exposure on the same doses used in adults, younger children may require doses greater than half the adult dose in order to achieve equivalent exposure. Simulations of different weight-related dosing regimens were conducted, to allow attainment of drug exposure above that identified as the threshold for efficacy. Recommendations of 2, 3 or 4 mg daily for children

weighing <= 25 kg, 25-40 kg or >40 kg, respectively, or a regimen of 2 mg in children <= 35 kg and 4 mg in children over 35 kg both appeared likely to provide adequate exposure equivalent to that seen in adults taking 4 mg daily. However, the efficacy of such regimens was not tested prospectively.

8.2 Drug-Drug Interactions

Drug-drug interactions were not explored in this submission.

8.3 Special Populations

In the neurogenic populations studied, sample sizes were too small to allow evaluation of the effects of gender, race, age or weight subgroups or metabolizer status. Review of the adverse effects experienced by the five poor metabolizers in these three studies does not reveal any indication of increased frequency or severity of adverse effects.

In the two studies on urinary urge incontinence, subgroups based on race were not evaluated, due to small numbers of non-Caucasians. Metabolizer status was not evaluated in the assessment of efficacy or safety; however, review of the adverse effects experienced by the 16 poor metabolizers identified in these two studies does not reveal any indication of increased frequency or severity of adverse events. Subgroup analyses of gender, age and weight groups were performed. Study 020 found significantly increased efficacy as measured by the primary endpoint in children between 4-6 years of age and in males, although this measure may be influenced by the lesser change experienced by the placebo group in these gender and age subgroups.

Safety was also evaluated with respect to gender, age and weight subgroups. In Study 020, the oldest and heaviest subgroups experienced a lower frequency of adverse events in the tolterodine group as compared to placebo, which may represent the effect of decreased drug exposure in these subgroups. Study 008 displayed a higher frequency of adverse events, particularly UTIs, in females, in both tolterodine and placebo-treated subjects. The frequency of adverse events decreased with increasing age group in both treatment groups. The lowest weight subgroup (<20 kg) had a higher incidence of adverse events in the tolterodine group, as compared to placebo and to tolterodine-treated subjects in the two higher weight groups. Again, this may represent association of greater numbers of adverse events with higher drug exposure.

8.4 Pediatrics

Pediatric subjects from ages 3 months to 15 years of age, inclusive, are represented in the study reports.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

See Section 16 for the sponsor's review of the pediatric literature available at the time of the NDA submission. The reviewer identified two additional reports published subsequent to the submission. They are described briefly in Section 7.1.4.

8.7 Post-marketing Risk Management Plan

Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

Following review of the complete efficacy supplement, the review concludes that:

- Studies (001, 002, and 003) in children with neurogenic lower urinary tract dysfunction were small, non-randomized, non-placebo-controlled trials. The urodynamic data from these trials were inconsistent and there was a general lack of dose-response trends. There were suggestions of improvement in the number of incontinence episodes in the tolterodine-treated groups
- Two large randomized, placebo-controlled trials failed to support the efficacy of tolterodine PR capsules for the treatment of urinary urge incontinence in neurologically normal pediatric patients.

9.2 Recommendation on Regulatory Action

It is recommended that the efficacy supplements for NDA 21-228 (SE8-006) receive an Approval.

9.3 Recommendation on Post-marketing Actions

Not applicable

9.4 Labeling Review

The sponsor proposes to maintain the current approved labeling for DETROL LA capsules, except for the proposed changes as outlined in the following Sections 9.4.1 through 9.4.5. No labeling changes were submitted for DETROL immediate release tablets (NDA 20-771).

9.4.1 Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section Pharmacokinetics in special populations – Pediatric subsection

The sponsor proposes to delete the following sentence:

~~The pharmacokinetics of tolterodine has not been established in pediatric patients.~~

And replace it with the following five paragraphs and table:

The pharmacokinetics of tolterodine immediate and extended release were evaluated in pediatric patients ranging in age from 5 to 15 years. Steady-state pharmacokinetic parameters are presented in Table 2.

Table 2. Summary of Mean (±SD) Pharmacokinetic Parameters of Detrol and it Active Metabolite (5-hydroxymethyl metabolite) in Pediatric Patients

	Tolterodine				5-hydroxymethyl metabolite			
	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)
5 – 10 yr † 2 mg bid EM (n=9)	1 (0.5 – 2)	11.5 (6.5)	2.6 (1.4)	2.0 (0.8)	2 (1 – 2)	8.5 (4.0)	2.8 (1.0)	2.6 (1.0)
5 – 10 yr 2 mg qd EM (n=302)	---- ‡	----	1.5 (1.6)	----	----	----	0.89 (0.39)	----
PM (n=20)	----	----	6.9 (3.2)	----	----	----	----	----
11 – 15 yr 4 mg qd EM (n=27)	3 (2 – 7)	3.7 (2.7)	1.8 (1.5)	15 (12)	4 (2-9)	2.4 (0.93)	1.3 (0.43)	14 (11)
PM (n=3)	3 (3 – 4)	19 (1.4)	14 (0.83)	29 (11)	----	----	----	----

Cmax = Maximum serum concentration; tmax = Time of occurrence of Cmax; Cavg = Average serum concentration; t1/2 = Terminal elimination half-life.

* Data presented as median (range).

† Dosed using immediate release tablets

‡ Not applicable.

At an equivalent daily dose of tolterodine immediate release, C_{avg} and C_{max} of tolterodine and the 5-hydroxymethyl metabolite were higher in children 5 to 10 years of age than in adults, while t_{max} and $t_{1/2}$ were similar between children and adults.

The elimination half-life appeared prolonged in pediatric patients 11 to 15 years of age as compared to the adult population. However, C_{avg}, C_{max} and t_{max} were comparable between the two populations at the 4-mg daily dose.

In patients ranging in age from 1 month to 4 years who received a 0.030 mg/kg twice-daily dose of an investigative tolterodine tartrate oral solution, tolterodine oral clearance (4.9 ± 4.5 L/h/kg) was higher and elimination half-life (1.5 ± 0.6 h) was shorter than values observed in children 5 to 10 years of age (CL/F = 3.7 ± 3.6 L/h/kg; $t_{1/2}$ = 2.2 ± 1.0 h).

Evaluation of the pharmacokinetic/pharmacodynamic relationship in children based on active moiety AUC suggests that administration of a tolterodine daily dose of 2 mg for patients weighing ≤35 kg or 4 mg for patients with body weight >35 kg would provide active moiety exposure that is similar to that in adults receiving 4 mg daily.

Medical Officer's Comments:

1) **It is the opinion of the reviewer that inclusion of pharmacokinetic data would imply efficacy of tolterodine in the pediatric population. It is recommended that the sponsor's proposed additions be rejected and the current statement, which the sponsor proposed to delete, be retained. This statement fairly reflects the fact that**

PK data obtained by the sponsor was at a dose not found to be efficacious in children.

2) **The reviewer recommends retaining the current numbering of all tables in the label, as the proposed additional tables are not acceptable.**

3) **The recommendation from the Division of Drug Marketing, Advertising and Communications (DDMAC) states that "DDMAC recommends deletion of the pediatric studies in the Pharmacokinetics in Special Populations, Clinical Studies, and Adverse Reactions sections of the PI in order to avoid an implied effectiveness in the pediatric patient population that has not been demonstrated."**

9.4.2 Sponsor Proposed Addition of Pediatric Patients Subsection to CLINICAL STUDIES Section

The sponsor proposes to add the following Pediatric Patients Subsection:

> DETROL LA 2 mg was evaluated in pediatric patients 5 to 10 years of age with the symptoms of urinary urgency, frequency and urge incontinence in two randomized, multicenter, placebo-controlled, double-blind, 12-week studies. A total of 487 patients received DETROL LA 2 mg in the morning and 224 received placebo. Efficacy in this population has not yet been demonstrated.

Medical Officer's Comments:

1) **The statement that efficacy has not "yet" been demonstrated is inappropriate. If there were to be any statement regarding clinical studies conducted in children, the brief general description of the studies could be retained, followed by the statement "Efficacy in this population was not demonstrated." It is recommended that such a description be placed in the PRECAUTIONS Section.**

2) **The recommendation from the Division of Drug Marketing, Advertising and Communications (DDMAC) states that "DDMAC recommends deletion of the pediatric studies in the Pharmacokinetics in Special Populations, Clinical Studies, and Adverse Reactions sections of the PI in order to avoid an implied effectiveness in the pediatric patient population that has not been demonstrated."**

9.4.3 Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection

The sponsor proposes to delete the following sentence:

> ~~The safety and effectiveness of tolterodine in pediatric patients has not been established.~~

And replace it with the following four sentences:

> The safety of DETROL LA has been demonstrated in two Phase 3 placebo-controlled, double-blind, 12-week studies of 486 pediatric patients ages 5 to 10. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults. The overall safety profile of tolterodine in this age group was comparable to that seen in adults (see **Clinical Studies** and **Adverse Reactions**).

Medical Officer's Comments:

1) **Given that there is off-label use in children of both Detrol and Detrol LA, there may be value in providing adverse event information obtained from the two phase 3 placebo-controlled studies. The following wording is suggested:**

"Efficacy in the pediatric population was not demonstrated.

A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5 to 10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA as compared to 0.9% of children treated with placebo."

2) **The recommendation from DDMAC states that "DDMAC recommends inclusion of the important safety information from these clinical studies in the Precautions-Pediatric Use section only, if clinically relevant, and including a prominent and concise statement about Detrol LA's ineffectiveness in this patient population. For example, 'The effectiveness of Detrol LA in children has not been demonstrated.'"**

3) **An additional comment from DDMAC is "Can the safety information in the Precautions-Pediatric Use section be qualified, i.e., 'The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults.' Terms such as "higher," "mild or moderate," and "lower" are vague and require context. This information would be useful to the reader."**

9.4.4 Sponsor Proposed Addition of Pediatric Studies Subsection to ADVERSE REACTIONS Section,

The sponsor proposes to add the following Pediatric Studies Subsection:

In two placebo-controlled clinical trials of DETROL LA Capsules, 710 pediatric patients ages 5 to 10 years were treated with DETROL LA (n=486) or placebo (n=224). Patients were treated with DETROL LA 2 mg for 12 weeks. The overall frequency of adverse experiences was almost identical in the DETROL LA and placebo treatment groups (48% and 49%, respectively). Urinary tract infection was the most common adverse event occurring at a rate greater than placebo reported by pediatric patients receiving DETROL LA. Dry mouth was only reported in 0.8% of patients treated with DETROL LA and in 1.8% of patients receiving placebo. A serious adverse event was reported by 1% (n=6) of pediatric patients receiving DETROL LA and 1% (n=2) of patients receiving placebo.

The frequency of discontinuation due to adverse events was 3% for both the DETROL LA and placebo treatment groups. Table 5 lists the adverse events reported in 1% or more of pediatric patients treated with DETROL LA 2 mg once daily in the 12-week studies.

Table 5 Incidence* (%) Of Adverse Events Exceeding Placebo Rate and Reported In ≥1% of Pediatric Patients Treated With DETROL LA (2 mg once daily) in Two 12-Week, Phase 3 Clinical Trials

Body System	Adverse Event	%DETROL LA (n=486)	%Placebo (n=224)
Gastrointestinal disorders	Abdominal pain	5	3
	Vomiting	4	2
	Diarrhea	3	1
	Constipation	2	1
Infections and infestations	Urinary tract infection	7	4
	Ear infection	1	0
Psychiatric disorders	Abnormal behavior	2	0
Respiratory, thoracic, and mediastinal disorders	Rhinitis	2	0

*in nearest integer.

Medical Officer's Comments:

1) **The reviewer proposes that this section remain absent from the Detrol LA label. The dose of Detrol LA from which these adverse event data are derived was not shown to be effective.**

9.4.5 Sponsor Proposed Changes to Revision date

The sponsor proposes to change the revision date listed at the very end of the physician insert from:

~~Revised July 2003~~

~~818-229-006~~

To:

Revised Month Year

Medical Officer's Comments:

1) **The proposed changes are acceptable to the reviewer.**

_____ April 12, 2004

Lisa M. Soule, MD Date

Medical Officer, DRUDP

Addendum:

Acceptable labeling was negotiated with the sponsor. There are no outstanding unresolved issues relating to this NDA submission.

_____ April 12, 2004

Lisa M. Soule, MD Date

Medical Officer, DRUDP

Appendix A: TRIALS IN NEUROGENIC BLADDER

10 CLINICAL TRIAL 583E-URO-0581-001

10.1 Summary

Title: "Phase I/II, open label, dose escalating, pharmacokinetic, pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine oral solution in children with detrusor hyperreflexia 1 month to 4 years of age," dated August 1, 2003, with Amendments dated August 24, 2001 and September 27, 2001.

Amendment #1 was dated August 24, 2001, and included the following changes:

- Added health economics assessments to the study
- Included a phone call from each study site at Visits 3 and 4 to approve the patient's dose escalation
- Added the volume of blood drawn at the PK blood draws to the Informed Consent form
- Revised the instructions for PK specimen collection
- Added instructions for collecting alpha$_1$-acid glycoprotein (AGP) specimens
- Deleted the protocol section dealing with in utero exposure.

Amendment #2 was dated September 27, 2001, and included the following changes:

- Replaced Appendix 6 to allow saline locks for blood sampling when appropriate
- Amended genotyping section of the protocol
- Clarified Informed Consent items including the dose escalation process at Visits 3 and 4 and data to be collected for the health economics assessment.

First patient enrolled: November 19, 2001

Last patient completed: May 28, 2003

Last follow-up: June 2, 2003

10.2 Objectives

The primary objective was to collect data on which to base dosing recommendations for the use of tolterodine in children less than five years of age with neurogenic bladder dysfunction, by comparing PK data on the active moiety with data obtained in adults and in children aged 5 to 10 years.

The secondary objectives were to estimate PK variables for tolterodine and DD 01 and to evaluate the PD (urodynamic) and clinical effects and safety of tolterodine oral solution in patients under age 5 with neurogenic bladder dysfunction. The tolterodine dose-effect (urodynamic) and the active moiety concentration-effect (urodynamic) relationships were to be determined. An estimate of the direct costs of detrusor hyperreflexia was to be made through the collection of health care utilization data.

10.3 Overall Design

This Phase 1/2, multicenter, 12-week treatment duration, open label, dose escalation, PK, PD, clinical effect and safety study evaluated the use of tolterodine tartrate oral solution in 19 pediatric subjects aged 3 months to 4 years for the treatment of detrusor hyperreflexia due to neurogenic conditions. Fifteen U.S. centers were eligible to enroll subjects, with a goal of enrolling 15 subjects total (at least 3 to be < 6 months old, approximately 6 to be aged 6 months to 2 years, and the remainder aged 2-4 years). Eight centers actually enrolled a total of 19 patients, of whom 17 had sufficient data for the

PK analyses. Subjects were enrolled within 3 months of a baseline urodynamic evaluation. Dosing was initiated at 0.03 mg/kg/day in two divided daily doses, which was maintained for four weeks. Following review of safety data, the dose was advanced to 0.06 mg/kg/day for four weeks and then to 0.12 mg/kg/day for four weeks. Urodynamic data, patient diary data, safety data and health care utilization data were collected at the end of each dose period. PK data were collected only at the 0.06 mg/kg/day dose level.

10.4 Study Procedures and Conduct

10.4.1 Schedule of Study Assessments

During the Screening/Baseline Visit (Visit 1), parental informed consent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after medical history, review of systems, physical examination, vital signs, EKG, urinalysis, serum chemistry profile and hematology labs were obtained. The parents were instructed in filling out the patient diary, to be done for the three days preceding entry into the study, once subjects had discontinued excluded drugs for a minimum of 3 days. Subjects who had not had urodynamic testing in the three months prior to study enrollment underwent this procedure at the time of screening. All patients returned to the clinic for study assessments according to the schedule presented in Table 14.

Blood samples for pharmacokinetic analysis were to be collected after completion of the four week 0.06 mg/kg/day dose period, after a total of 8 weeks of treatment. Urodynamic measurements and patient diary completion were to be performed at baseline (at the end of the washout period) and repeated at the end of each four-week dose period (two hours after receiving the last morning dose of that dose level). Any subject who withdrew prior to completion of a dosing level was encouraged to complete the patient diary and evaluation before stopping the medication.

Any subject who developed a clinical UTI during treatment was treated with an appropriate antibiotic for 7 days. Urodynamic testing and patient diary completion were postponed until 3 days after the completion of antibiotic treatment; patients were maintained on their current dose level for up to two additional weeks in cases of delayed urodynamic testing.

Table 14 Study 583E-URO-0581-001 Schedule of Study Assessments

	Visit Number (day)/ Visit Description					
	1 (Day -6 to Day -14)	2 (Day 1)	3 (Day 28)	4 (Day 58)	5 (Day 84)	6 (Day 91)*
Activity	Screening	Baseline	4 weeks	8 weeks (PK visit)	12 weeks	13 weeks
Informed consent	X					
Medical history	X					
Review of systems and physical examination	X	X	X	X	X	
Inclusion/exclusion criteria	X					
Demographic data	X					
Chemistry and hematology	X		X	X	X	
Urinalysis	X	X	X	X	X	
Dispense patient diary	X	X	X	X		
Return completed diary		X	X	X	X	
Urodynamic testing	X	X	X	X	X	
Adverse events			X	X	X	X
Tolterodine intake†		X	X	X	X	
Blood sample for AGP‡				X		
Blood sample for PK§				X		
Blood sample for genotyping¶			X			
ECG#	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	
Weight	X	X	X	X		
Health care utilization			X	X	X	X

* Phone call 1 week after discharge and, in the case of unresolved AEs, contact 2 weeks after last dose.

† Study medication given to patient to begin intake on the following day. Tolterodine oral solution doses of 0.030 (first 4 weeks), 0.060 (second 4 weeks), and 0.120 mg/kg/day (third 4 weeks) to be administered in divided doses (at approximately 8 AM and 8 PM) from Day 1 to 84.

‡ Sample collected in connection with the blood sample for measuring tolterodine and DD 01.

§ PK samples collected pre-dose and at 0.5, 1, 2, 6 and 8 hours after receiving the 0.030 mg/kg morning dose (at the 0.060 mg/kg/day dosage level).

¶ Sample collected at same time as that taken for chemistry and hematology.

One ECG at screening, one ECG every 15 minutes for 1 hour (4 total) at Visits 2, 3, and 5, and one ECG coincident with each blood draw at Visit 4 (6 total).

AGP=α_1-acid glycoprotein; ECG=electrocardiogram; PK=pharmacokinetics.

Source: Table 1, *5.3.4.2.1, p28*

10.4.2 Study Drug

10.4.2.1 Dose Selection

The drug studied was an investigational product, tolterodine tartrate oral solution, 1 mg/5 ml, which is not commercially available. Three escalating doses (0.03 mg/kg/day, 0.06 mg/kg/day and 0.12 mg/kg/day) were given to all subjects at four week intervals. The mid-range dose was chosen to approximate the exposure of adults receiving 2 mg BID of the tolterodine IR tablet, bracketed by 0.5 and 2 times this dose to explore the dose-response relationship. Dosing was BID, at approximately 8 am and 8 pm.

10.4.2.2 Choice of Comparator

This was an open-label trial; there was no placebo or comparator.

10.4.2.3 Assignment to Study Drug

There was no randomization in this study; all subjects received all doses sequentially.

10.5 Patient Population

10.5.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1) Male or female between 1 month and four years of age, inclusive.

2) Stable neurological disease (meningomyelocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management of urinary drainage.

3) Body weight or body mass index (BMI) within normal range (between the 5^{th} and 95^{th} percentiles), according to the CDC Growth and BMI Charts for the United Sates.

4) Physiologically normal, apart from the stable neurological disease, with no acute illnesses on the basis of the pre-study physical exam

5) Signed informed parental/guardian consent, with signed informed assent by the patient as appropriate.

Exclusion Criteria

1) Any condition which, in the investigator's opinion, made the patient unsuitable for inclusion.

2) Recent history of clinically significant cardiovascular, hepatic, renal, gastrointestinal or hematological disease, or psychiatric disorder.

3) Suspicion of psychological component of patient's micturition/incontinence problems.

4) Known anatomic abnormalities in the urinary tract, with the exception of vesicoureteral reflux <=grade III.

5) History of management with an indwelling urinary catheter for > 6 months or within 4 weeks of participation in the study.

6) Clinically significant urinary tract infection during the four weeks preceding participation in the study.

7) Any condition contraindicating anticholinergic therapy.

8) Known hypersensitivity to tolterodine or its excipients or history of adverse drug reaction to anticholinergic drugs.

9) Treatment with other drugs with significant anticholinergic properties deemed by the investigator to have significant effects on the lower urinary tract, or treatment with drugs affecting bladder

function up to 3 days before start of baseline study measurements, or treatment with potent CYP3A4 inhibitors up to 7 days before the start of any pre-study measurements.

10) History of clinically significant hypersensitivity or severe allergy.

11) Parent/guardian unable to understand or cooperate with given information.

12) Participation in a clinical study within 1 month preceding participation in this study or previous participation in this study.

10.5.2 Demographics and Baseline Disease Characteristics

Eight US sites enrolled between 1 and 5 patients each, for a total of 19 subjects. Two patients (109, a four year-old white male, and 118, a four year-old white female) did not have data available at the PK blood draw; therefore, the PK population for this study is 17 subjects. Baseline demographic characteristics for the 19 subjects are summarized in Table 15. The trial included 10 males and 9 females. The majority of the patients (>80%) in the trial were Caucasian. The age breakdown is: 3 subjects less than 6 months, 6 between 6 months and 2 years, and 10 between 2 and 4 years. Eighteen subjects had myelomeningocele; the remaining patient had a spinal cord injury. Three subjects had vesicoureteral reflux at baseline; all were in Grades I-III. All but one subject in the PK population were extensive metabolizers. The median weight was 11.6 kg, ranging from 5.4 to 19.3 kg.

Table 15 Baseline Demographics

Demographic Characteristic		Safety Population N=19	PK Population N=17
Sex	Male , n (%)	10 (52.6)	9 (52.9)
	Female, n (%)	9 (47.4)	8 (47.1)
Age (years)	Mean (SD)	2.4 (1.7)	2.2 (1.7)
	Median (min, max)	2.0 (0.3, 4.9)	1.8 (0.3, 4.9)
	Not reported	0	0
Age (months)	Mean (SD)	28.3 (20.5)	25.9 (20.4)
	Median (min, max)	24.2 (3.2, 59.1)	21.8 (3.2, 59.1)
	Not reported	0	0
Age group	< 6 months , n (%)	3 (15.8)	3 (17.6)
	6 months to <2 years, n (%)	6 (31.6)	6 (35.3)
	2 to <5 years , n (%)	10 (52.6)	8 (47.1)
Race	White , n (%)	16 (84.2)	14 (82.4)
	Black , n (%)	1 (5.3)	1 (5.9)
	Not listed, n (%)	2 (10.5)	2 (11.8)
Genotype	Extensive Metabolizer , n (%)	17 (89.5)	16 (94.1)
	Poor Metabolizer , n (%)	1 (5.3)	1 (5.9)
	Patients not reporting, n (%)	1 (5.3)	

Source: Table T5.
Note: Age is defined as age at screening (visit 1). Patient 103, who was just 6.0 months old at screening, is included in the '<6 months' age group. For Patients 101, 103, 110 and 116 the results of genotyping were missing; however Patient 101 is classified as a poor metabolizer and Patients 103, 110 and 116 are classified as extensive metabolizers based on the bioanalytical results.

Source: Table 4, *5.3.4.2.1, p 53*

10.5.3 Withdrawals, protocol violations and compliance

Two patients discontinued participation early:

- Patient 115, a 10-month old female, discontinued after 67 days on treatment (29 days on 0.03 mg/kg/day and 38 days on 0.06 mg/kg/day) due to an adverse event (increase in AST from baseline of 61 IU/L to 111 IU/L; 1.85 times the upper limit of normal).

- Patient 118, a four year-old female, withdrew consent after 27 days on treatment (19 days on 0.03 mg/kg/day and 8 days on 0.06 mg/kg/day) as a result of a chronic UTI unresponsive to oral antibiotics.

There were one major protocol and six minor violations in inclusion criteria:

- Patient 117 did not require intermittent catheterization (major)
- Patients 106, 108, 110, 116, 118 and 119 had BMI < 5^{th} percentile (minor)

There were four major protocol violations in study conduct:

- Patient 110 received 0.04 mg on the PK day, rather than the planned 0.24 mg. This patient's data were excluded from the PK statistics.
- Patient 117 did not require intermittent catheterization, as specified in the inclusion criteria. This patient also received the third dose level for 66 days due to a delay in urodynamic assessment. This patient's data were included in the PK statistics.
- Patient 111 did not document dose intake for two of the three days preceding the PK day. This patient's data were included in the PK statistics.
- Patient 109 had no PK samples after multiple failed sampling attempts.

Minor deviations included:

- Patient 107 took only half the morning dose two days prior to the PK day, and did not take the afternoon/evening dose on the day prior to the PK day. This patient's data were included in the PK statistics.
- Patient 105's PK samples were received thawed by the lab. Stability studies demonstrated stability of tolterodine and DD 01 in thawed samples for up to seven days. This patient's data were included in the PK statistics.

Compliance was assessed by recording in the patient diary the dates and times of the doses for the three days prior to Visits 3, 4 and 5. Additionally, the bottles of tolterodine were returned at the end of each four-week dosing period, and the amount used was measured and compared to the expected use. Compliance was defined as actual use >75% expected use. There were no patients documented as having poor medication compliance.

Medical reviewer comments:

1) No individual treatment compliance data are provided in the study report.

10.6 Efficacy

10.6.1 Key Efficacy Assessments

Clinical effect endpoints included both data obtained by urodynamic evaluation and data derived from patient diaries. The urodynamic variables were:

- volume to first detrusor contraction of >10 cm H_2O pressure,
- functional bladder capacity and leak point pressure,
- intravesical volume at 20 and 30 cm H_2O pressure,
- maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure),
- bladder compliance and
- percent change in cystometric capacity

Dose-PD effects for tolterodine were determined by assessing the urodynamic parameters at each of the three dose levels; concentration-PD effects for the active moiety were determined by assessing the urodynamic parameters at the PK dose (0.06 mg/kg/day). The urodynamic variables were characterized by descriptive statistics, change from baseline and percent change from baseline at weeks 4, 8 and 12. Three of the urodynamic variables were normalized in relation to each patient's theoretical bladder capacity (calculated by [(2 + age in years) x 30 ml]): volume to first detrusor contraction, functional bladder capacity and intravesical volumes.

The patient diary variables were:

- mean number of catheterizations or micturitions per 24 hours,
- mean volume per catheterization/micturition and
- mean number of incontinence episodes per 24 hours, with the incontinence episodes further classified as to severity on a four point scale

and were based on means derived from three-day diary recordings done at baseline and at each dose period (weeks 4, 8 and 12).

10.6.2 Primary Efficacy Endpoint Analysis

In Study 001, the primary efficacy endpoints were assessed by urodynamic testing and completion of daily diaries. Some of the urodynamic variables (maximal cystometric capacity and bladder wall compliance) were unable to be obtained for all subjects due to patient discomfort during the procedure. Table 16 displays the baseline urodynamic variables and the mean change from baseline at each of the three dose periods. Changes were not noted in leak point pressure or in intravesical volume and bladder wall compliance at 30 and 40 cm H_2O pressures. There was a tendency for more marked change from baseline in the two higher dose categories for volume to first detrusor contraction, functional bladder capacity and intravesical volume and bladder wall compliance at 20 cm H_2O pressure, however, there was not a clear dose-response pattern, and many of the confidence limits for these change estimates contain zero. In exploration of the exposure-effect relationship, there was no correlation between AUC_{0-12} of the active moiety and change from baseline in either volume to first detrusor contraction or functional bladder capacity.

Table 16 Study 001 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)	42.6 (21.1)	50.9 (30.8)	71.3 (43.6)	2.1 (1.1)	1.7 (1.0)	1.8 (1.1)
	N	19	19	19	19	13	12	19	13	12
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)	2.4 (28.6)	-3.2 26.4)	-10 (36.0)	0.1 (1.4)	-0.1 (0.9)	-0.3 (0.9)
	N	17	19	18	18	12	9	18	12	9
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	15.9 (30.5)	**31.7 (54.7)**	-8.4 (14.4)	**37.1 (52.2)**	24.1 (45.7)	46.0 (74.0)	**1.9 (2.6)**	0.8 (1.5)	1.2 (1.8)
	N	16	18	16	14	8	6	14	8	7
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**34.4 (61.4)**	32.5 (63.7)	-3 (14.3)	**29.2 (46.9)**	27.2 (59.5)	12.8 (40.1)	**1.5 (2.3)**	0.9 (2.0)	0.3 (1.0)
	N	17	17	14	15	9	5	15	9	5

VFDC= Volume to first detrusor contraction > 10 cm H_2O
FBC = Functional bladder capacity
LPP = Leak point pressure
IVV= Intravesical volume
BWC= Bladder wall compliance
Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Tables 10-12, *5.3.4.2.1, pp 64-66*

The patient diary data is displayed in Table 17. As expected in patients on a scheduled catheterization regimen, there was no change in the number of daily catheterizations/micturitions. Dose-related improvements in mean daily incontinence episodes and mean volume voided were seen at the higher two doses, in a dose-response manner. There was, however, no relationship between AUC_{0-12} of the active moiety and change from baseline in any of the diary variables.

Table 17 Study 001 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean	4.8	5.2	34.9
	(SD)	(1.4)	(1.9)	(16.1)
	N	18	18	18
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean	-0.1	-0.2	5.7
	(SD)	(1.1)	(2.0)	(19.9)
	N	18	18	18
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean	-0.2	**-0.9**	**13.2**
	(SD)	(1.1)	**(1.9)**	**(24.0)**
	N	17	18	17
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean	-0.1	**-1.2**	**21.7**
	(SD)	(0.8)	**(1.7)**	**(25.7)**
	N	16	17	16

Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Table 13, *5.3.4.2.1, p 70*

10.7 Pharmacokinetic Assessments

Pharmacokinetic endpoints were the serum PK of the active moiety, including AUC_{0-12}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12}, F_{ext}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints. Samples were taken at visit 4, at the end of the 0.06 mg/kg/day dose period and were obtained pre-dose, and at 0.5, 1, 2, 6 and 8 hours post dose.

10.7.1 Pharmacokinetic Data Summary (PK Population)

Table 18 shows the distribution of the total daily dose of tolterodine in the Study 001 subjects. The mean daily dose at the PK dose level was 0.71 mg/day.

Table 18 Total Daily Dose by Dose Period and Age Group

	Period 1 0.030 mg/kg/day (N=19)			Period 2 0.060 mg/kg/day (N=19)			Period 3 0.120 mg/kg/day (N=17)		
Total Daily Dose in mg:	<6 mos	6 mos to <2 yrs	2 to <5 yrs	<6 mos	6 mos to <2 yrs	2 to <5 yrs	<6 mos	6 mos to <2 yrs	2 to <5 yrs
<=0.2 mg	2	1	.	.	.	.	.	.	.
>0.2-0.5 mg	1	5	9	3	1	.	.	.	.
>0.5-1.0 mg	.	.	1	.	5	9	2	1	.
>1.0-2.0 mg	.	.	.	.	.	1	1	4	8
>2.0-3.0 mg	.	.	.	.	.	.	.	.	1
Mean (mg)	0.34			0.71			1.48		
Median (mg)	0.34			0.70			1.52		
Min, Max (mg)	0.16, 0.65			0.38, 1.31			0.80, 2.64		

Source: Table 6, *5.3.4.2.1, p 55*

Pharmacokinetic parameters for the active moiety are displayed in Table 19, and for tolterodine and DD 01 in Table 20.

Table 19 Pharmacokinetic Parameters for the Active Moiety after the 0.03 mg/kg BID dose (0.06 mg/kg/day Regimen) N=16

Parameter	Statistic	Active moiety
AUC_{0-12} (nM*hr)	Mean (SD)	5.9 (2.6)
	Median (min, max)	5.7 (2.9, 12.0)
Fext (%)	Mean (SD)	6.7 (4.3)
	Median (min, max)	5.4 (2.0, 18.1)
C_{max} (nM)	Mean (SD)	1.66 (0.61)
	Median (min, max)	1.59 (0.82, 2.76)
C_{min} (nM)	Mean (SD)	0.08 (0.11)
	Median (min, max)	0.04 (0.00, 0.34)

Source: Table T14b.
Note: Patient 110 excluded due to incorrect PK dose. Cmin for all but 2 patients was at time 0; Cmin for two patients (Patients 101 and 104) was at 8 hr.

Source: Table 7, *5.3.4.2.1, p 57*

Table 20 Pharmacokinetic Parameters for Tolterodine and DD 01 after the 0.03 mg/kg BID dose (0.06 mg/kg/day Regimen)

		Tolterodine		DD 01
Parameter	Statistic	Extensive Metabolizers (n=12)	Poor Metabolizers (n=1)	Extensive Metabolizers (n=15)
AUC_{0-12} (µg*hr/L)	Mean (SD)	8.5 (8.0)	92.4	7.9 (3.9)
	Median (min, max)	7.8 (1.4, 30.3)		8.5 (3.0, 15.6)
F_{ext} (%)	Mean (SD)	3.2 (3.1)	18.1	6.3 (3.4)
	Median (min, max)	2.1 (0.3, 8.8)		5.7 (2.1, 13.1)
C_{max} (µg/L)	Mean (SD)	2.86 (2.75)*	13.70	2.23 (1.12)
	Median (min, max)	2.49 (0.43, 10.40)*		2.17 (0.79, 5.13)
t_{max} (hr)	Mean (SD)	1.02 (0.59)*	1.88	1.12 (0.53)
	Median (min, max)	0.92 (0.47, 2.00)*		1.00 (0.47, 2.00)
C_{min} (µg/L)	Mean (SD)	0.051 (0.102)*	5.510	0.071 (0.101)
	Median (min, max)	0.000 (0.000, 0.360)*		0.000 (0.000, 0.317)
$t_{1/2,z}$(hr)	Mean (SD)	1.52 (0.58)	4.54	2.09 (0.55)
	Median (min, max)	1.34 (0.91, 2.55)		1.92 (1.44, 3.21)
V_{ss}/F (L)	Mean (SD)	113 (93)	19	NC
	Median (min, max)	102 (19, 291)		
CL/F (L/hr)	Mean (SD)	58 (50)	3	NC
	Median (min, max)	40 (6, 177)		
V_{ss}/F (L/kg)	Mean (SD)	9.31 (7.19)	1.53	NC
	Median (min, max)	5.26 (2.01, 22.89)		
CL/F (L/hr/kg)	Mean (SD)	4.91 (4.52)	0.23	NC
	Median (min, max)	2.66 (0.67, 14.24)		

Source: Table T14a.
*n=15.
Note: Patient 110 excluded due to incorrect PK dose. For tolterodine, C_{min} at time 0 except Patients 101 and 104 where C_{min} was at 8 hr. For DD 01, C_{min} at time 0 except Patient 104 with C_{min} at 8 hr. The weight at visit 4/week 8 was used to calculate the V_{ss}/F (L/kg) and CL/F (L/hr/kg).
NC=not calculated.

Source: Table 8, *5.3.4.2.1, p 58*

Comparison of AUC_{0-12} and C_{max} for this pediatric population, the 5-10 year olds in study 044 and adults receiving 4 mg of tolterodine IR BID was made by the reviewer and is presented in Table 21.

Table 21 AUC_{0-12} and C_{max} of Tolterodine and the Active Moiety in Pediatric Patients and Adults on Tolterodine IR

Parameter	Peds 1 mo-4 years[1] 0.03 mg/kg/BID syrup Mean dose 0.7 mg/day	Peds 5-10 years (Study 044)[2] 0.5 mg BID tablet (1 mg/day)	Adults (healthy volunteers)[3] 2 mg BID tablet (4 mg/day)
Tolterodine* AUC_{0-12} (ug*hr/L) Mean (SD)	8.5 (8.0) (N=12)	11.2 (13.5) (N=9)	N/A
Tolterodine* C_{max} (ug/L) Mean (SD)	2.9 (2.8) (N=12)	3.4 (3.0) (N=9)	N/A
Active Moiety** AUC_{0-12} (ug*hr/L) Mean (SD)	5.9 (2.6) (N=16)	7.2 (2.4) (N=10)	14 (6.4) – 15 (4.3) (Two studies, N = 24 and 18, respectively)
Active Moiety** C_{max} (ug/L) Mean (SD)	1.7 (0.6) (N=16)	1.8 (0.8) (N=10)	2.8 (0.8) – 3.4 (1.7) (Two studies, N = 18 and 24, respectively)

*Extensive metabolizers only

** Extensive and poor metabolizers

Source: [1]Table 7 & 8, *5.3.4.2.1, pp 57-58*, [2]Tables 10.3.4.1.2, 10.3.4.1.3 and 10.3.3.2.1, *5.3.3.2.3, pp 51, 53* and [3]Table 11.1, *5.3.3.2.3, p 62*

Drug exposure, measured by AUC, is lower in the current study and formulation than that seen in Study 044, which used a higher daily dose in tablet form. Adjusting for total daily dose, an AUC of 7.8 for tolterodine would be expected in Study 001, so there is a good approximation of the pharmacokinetics seen in older children receiving the immediate release tablet. Similarly, the Cmax is lower in the current study than in Study 004, as would be expected with lower daily dosing. Values for the active moiety are reasonably equivalent in the two pediatric age groups. Compared to adults receiving a four-fold higher dose, the PK values for the active moiety in each pediatric age group are approximately 50% of that seen in adults.

Medical reviewer's comment:

Tolterodine PK data for adults on 4 mg/day of immediate release tablets are not presented in the study report.

10.8 Safety

10.8.1 Safety Measurements

The safety population comprised all subjects who received at least one dose of medication; all 19 enrolled subjects are included. A safety evaluation was performed prior to escalation to the next dose. Adverse events were coded according to the Medical Dictionary for Regulatory Activity (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events, classified as serious or non-serious
- Laboratory evaluations (hematology, clinical chemistries, and urinalysis) at Screening and Visits 3, 4 and 5
- 12-lead ECG at each visit (four ECGs obtained at Visits 2, 3 and 5; six at Visit 4). The four ECGs obtained at dose periods 1 and 3 were measured about two hours after dosing; the six taken at dose period 2 were taken at 0, 0.5, 1, 2, 6 and 8 hours after dosing.
- Physical examination and vital signs at each visit
- Gastrointestinal function based on baseline review of systems and patient diary recordings

10.8.2 Serious adverse events

Deaths: there were no deaths

Premature termination due to adverse events: one patient (115) terminated prematurely from the study due to an increase in AST (from 61 IU/L at screening [upper limit of normal range = 60 IU/L] to 111 IU/L on day 67; the AST decreased to 65 IU/L within two weeks of study discontinuation). This was considered a non-serious adverse event, and was considered related to the study medication.

Medical Reviewer's comment:

> **Elevation of AST in one of only 19 subjects is of concern. This case is confounded by an elevated (although minimally) transaminase level at baseline.**

Serious adverse events: Two serious adverse events occurred; both were considered unrelated to the study medication. One patient (114) with a ventriculo-peritoneal shunt placed at birth experienced scalp swelling on day 9 and underwent a shunt revision without discontinuation in the study. A second patient (118) experienced a pseudomonas UTI on day 20, which was unresponsive to oral antibiotics. The parents withdrew the subject from the study on day 27. The UTI ultimately required hospitalization with 10 days of IV antibiotics to resolve. The patient had a previous history of pyelonephritis and UTI.

Medical Reviewer's comment:

> **Narratives for the two serious adverse events were reviewed. The UTI could be related to study drug if larger volumes per void on treatment resulted in an increased tendency to reflux urine. However, the patient was being catheterized multiple times each day and had a history of chronic UTI, so the reviewer considers the serious adverse event of UTI to be unlikely to be related to study drug.**

10.8.3 Frequent adverse events

All subjects but one reported at least one adverse event, with approximately equal frequency at each dose period (N=12 during dose period 1, N=13 during dose period 2, N=11 during dose period 3). The most frequent adverse events were constipation, upper respiratory tract infections, UTIs and cough. Table 22 presents the adverse events occurring in more than 2 subjects in the safety

population. The only adverse events considered to be treatment related were four of the cases of constipation and the AST elevation.

Table 22 Adverse Events Reported by Two or More Patients in the Safety Population

System Organ Class (MedDRA)	Preferred Term (MedDRA)	Number (%) of Patients
Gastrointestinal disorders	Constipation	5 (26.3)
Infections and infestations	Upper respiratory tract infection NOS	5 (26.3)
Infections and infestations	Urinary tract infection NOS	4 (21.1)
Respiratory, thoracic and mediastinal disorders	Cough	4 (21.1)
Infections and infestations	Nasopharyngitis	3 (15.8)
Infections and infestations	Otitis media NOS	2 (10.5)
Respiratory, thoracic and mediastinal disorders	Rhinitis NOS	2 (10.5)
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	2 (10.5)
Respiratory, thoracic and mediastinal disorders	Sinus congestion	2 (10.5)

Source: Table T42.
Note: For patients reporting the same adverse event on more than one occasion, the event was only counted once. Percentage (%) is based on total number of patients in safety population.
NOS=not otherwise specified.

Source: Table 15, *5.3.4.2.1, p 75*

Anticholinergic adverse events were reported by 6 (32%) of the subjects, with constipation (5 patients) and vomiting (1 patient) the most frequently reported events. There were no reports of dry mouth.

10.8.4 Laboratory Values

The serum chemistry, hematology, and urinalysis test results were reviewed. Shifts from baseline in laboratory parameters are displayed in Table 23. No clinically significant changes in the laboratory values were noted aside from the one subject who discontinued secondary to elevated AST, which rose steadily over each dose period.

Table 23 Shifts from Baseline in Laboratory Safety Variables

Laboratory Variable	WEEK 4 (DAY 28)			WEEK 8 (DAY 56)			WEEK 12 (DAY 84)		
	Up	Down	Missing	Up	Down	Missing	Up	Down	Missing
Alanine Aminotransferase (ALT/SGPT)	3	.	3	1	.	.	1	.	.
Alkaline Phosphatase	1	.	3	.	.	.	.	.	.
Aspartate Aminotransferase (AST/SGOT)	2	.	3	1	.	.	.	.	.
Bilirubin, Total	.	1	3	.	.	1	.	.	.
Creatinine	1	.	4	.	1	1	.	.	1
Erythrocytes (Red Blood Cells, RBC)	1	2	2	.	3	1	1	1	2
Hemoglobin, mass concentration	.	.	2	.	3	1	.	2	2
Leukocytes (White Blood Cells, WBC)	2	.	2	.	1	1	.	.	2
Platelet Count	1	.	2	2	.	1	1	.	2
Potassium (K)	.	.	3	.	.	.	.	.	.
Sodium (Na)	.	3	3	1	3	.	1	2	.
Thyroid-Stimulating Hormone (TSH)	.	.	3	1	.	.	.	.	3

Source: Table T68, *5.3.4.2.1, p 253*

Medical Reviewer's comments:

1) Table 18 does not include values that were outside the normal range at baseline and continued in the same direction at dosing.

2) Two apparent errors were evident on review of the individual subjects' laboratory data. Subject 107 was reported to have a hemoglobin value at week 8 of -13.8. This was reported as a low value. However, review of the subject's hemoglobin trend (14.8 at baseline, 14.2 at week 4, 13.6 at week 12) suggests that this should actually be recorded as 13.8, or slightly elevated. Subject 119 is reported to have a creatinine of 50 at week 4. This subject's preceding and succeeding values were 0.2 at baseline, week 8 and week 12.

10.8.5 ECGs

Two subjects had ECGs read as abnormal and clinically significant at screening and baseline, one (107) with an ectopic atrial rhythm and one (106) with a sinus bradycardia. Both findings were considered by the investigator to be within the limits of pediatric normality, allowing the subjects to be included in the trial Another two subjects had baseline abnormal findings, both sinus bradycardias, that were not judged to be clinically significant. At the treatment visits, sinus bradycardia was seen in approximately equal numbers of subjects at each dose period, and sinus tachycardia was seen predominantly at dose period 2 (Table 24).

Table 24 ECG Rhythms by Dose Period

	Baseline N=19	Period 1 0.030 mg/kg/day N=19	Period 2 0.060 mg/kg/day N=19	Period 3 0.120 mg/kg/day N=17
Normal Sinus Rhythm	15	14	12	11
Sinus Bradycardia	3	5	4	4
Sinus Tachycardia	0	0	3	1
Ectopic Atrial Rhythm	1	1	1	1
Not reported	0	0	0	2

Source: Table T59, *5.3.4.2.1, p 236*

Abnormal QT findings had been defined a priori as a QT interval exceeding 500 msec on any ECG or a change from baseline QT interval of greater than 60 msec. Mean uncorrected and corrected (Fridericia) QT intervals showed no significant change over dose periods. Both corrected and uncorrected QT intervals tended to decrease slightly at dose periods 1 and 2; mean values at dose period 3 were almost identical to values at baseline (Table 25).

Table 25 Corrected and Uncorrected QT Intervals by Dose Period

		QT (msec)	QTc Fridericia (msec)	QTc Bazett (msec)
Baseline	Mean (SD)	281.4 (27.5)	353.3 (18.0)	396.5 (15.6)
	Median (min-max)	282.3 (238.5 to 334.8)	352.8 (324.8 to 387.0)	396.8 (369.8 to 423.5)
	Not reported	0	0	0
Period 1: 0.030 mg/kg/day	Mean (SD)	278.0 (21.9)	349.6 (14.0)	392.4 (14.7)
	Median (min-max)	272.0 (228.3 to 321.0)	353.8 (320.5 to 374.0)	394.3 (353.3 to 412.5)
	Not reported	0	0	0
Period 2: 0.060 mg/kg/day	Mean (SD)	272.9 (20.6)	349.1 (14.5)	395.4 (15.1)
	Median (min-max)	273.2 (225.8 to 307.8)	347.2 (324.8 to 376.0)	392.5 (371.5 to 432.5)
	Not reported	0	0	0
Period 3: 0.120 mg/kg/day	Mean (SD)	281.6 (19.9)	353.5 (12.3)	396.4 (11.4)
	Median (min-max)	282.3 (233.8 to 317.5)	353.5 (326.5 to 374.0)	393.8 (378.5 to 416.8)
	Not reported	2	2	2
Change from Baseline to period 1	Mean (SD)	-3.4 (16.0)	-3.8 (13.6)	-4.2 (15.1)
	Median (min-max)	-7.3 (-30.3 to 24.5)	-3.3 (-31.0 to 22.3)	-6.0 (-31.0 to 22.0)
	H-L (95% c.i.)*	-3.3 (-13.0, 4.6)	-4.1 (-10.8, 3.3)	-4.0 (-12.0, 3.6)
	Not reported	0	0	0
Change from Baseline to period 2	Mean (SD)	-8.5 (18.9)	-4.2 (16.3)	-1.2 (17.5)
	Median (min-max)	-11.6 (-43.3 to 32.8)	-5.6 (-32.0 to 31.3)	-2.7 (-33.4 to 29.8)
	H-L (95% c.i.)*	-9.9 (-17.8, 0.4)	-5.4 (-12.9, 3.1)	-1.2 (-9.7, 8.2)
	Not reported	0	0	0
Change from Baseline to period 3	Mean (SD)	-3.4 (21.6)	-1.9 (16.3)	-1.2 (15.6)
	Median (min-max)	-3.3 (-49.8 to 35.5)	-0.5 (-31.0 to 31.8)	1.0 (-26.0 to 27.8)
	H-L (95% c.i.)*	-2.4 (-15.4, 9.3)	-1.5 (-10.4, 6.1)	-0.8 (-9.4, 5.9)
	Not reported	2	2	2

Source: Table T54a, *5.3.4.2.1, pp 224-225*

There was only one QT interval greater than 450 msec in period 2 and this was noted only with the Bazett correction. QT prolongation greater than 30 msec beyond baseline was seen in 1.4 to 7.5% of ECGs, depending on the dose period and the correction used (Table 26). Changes greater than 30 msec in uncorrected QT occurred in one subject at dose period 1, and two subjects each in dose periods 2 and 3. The highest change was 48.5 msec, at dose period 2. Using QTcF, only one subject had an elevation >= 30 msec at dose period 1, three at dose period 2 and two at dose period 3, with a maximum of 51 msec. The QTcB correction resulted in higher frequencies of change >= 30 msec, with two patients showing increases at dose period 1 (and another subject at an unscheduled visit during dose period 1), six at dose period 2 and 2 at dose period 3, with a maximum increase of 53 msec.

Table 26 Change from Baseline QT Interval by Dose Period

		Period 1 N=19		Period 2 N=19		Period 3 N=17	
		n	%	n	%	n	%
QT	< 30 msec	72	98.6	103	96.3	64	94.1
	>= 30 to <60 msec	1	1.4	4	3.7	4	5.9
QTcF	< 30 msec	72	98.6	103	96.3	65	95.6
	>= 30 to <60 msec	1	1.4	4	3.7	3	4.4
QTcB	< 30 msec	70	95.9	99	92.5	64	94.1
	>= 30 to <60 msec	3	4.1	8	7.5	4	5.9

Note: Ns refer to ECGs, not to subjects

Source: Table T65, *5.3.4.2.1, p 249*

Medical Reviewer's comment:

1) **The definition of tachycardia was > 100 beats/minute. This is inappropriate in this age group, where the mean heart rate ranges from 108-141 beats/minute[3]**
2) **While 13 cases of sinus bradycardia are reported over the three dose periods, there were only 2 cases judged clinically relevant, both at dose period 1. One case occurred in subject 106, who had had abnormal screening/baseline values; one occurred de novo on only one recording on this visit and was not seen at subsequent visits.**
3) **The ectopic atrial rhythm see in subject 107 at screening and baseline persisted intermittently throughout the trial, but was not judged to be clinically relevant after the baseline period.**
4) **All cases of sinus tachycardia were judged to be clinically significant. Subject 114 was noted to have this finding at the screening visit, at one recording at dose period 2 and two recordings at dose period 3. The two other subjects with sinus tachycardia manifested this finding only at visit 8.**
5) **The criteria for defining a QT interval or interval change as abnormal in this study (>500 msec, >60 msec) are commonly used as thresholds for discontinuation from a trial. The results are reported by the more stringent criteria of interval >= 450 msec and change >= 30 msec. This is appropriate as the upper limit of normal QT interval in children is reported to be 450 msec in males and 460 msec in females[4]. The single QTcB interval greater than 450 was 458 and occurred on only one of six recordings at dose period 2.**
6) **With no placebo or positive control data, interpretation of the QT interval data is difficult. The Fridericia data show no significant mean changes from baseline. The highest proportion of QT interval change from baseline > 30 msec occurred with the Bazett correction, which is known to overcorrect at higher heart rates (i.e., as seen in children).**

10.8.6 Vital Signs

Blood pressure, pulse, temperature and respiratory rate were obtained at each visit; however, neither composite nor individual data are reported.

Medical Reviewer's comment:

No data on vital signs evaluations are presented.

10.8.7 Gastrointestinal Function

Gastrointestinal function was assessed at each visit by patient diary reports of number of bowel movements over three days along with assessment of their consistency. Parents were also asked to comment on the subject's bowel regimen and any changes noted over the four week treatment interval. Table 27 presents the mean number of daily bowel movements and mean consistency over each treatment period. There was a trend toward fewer daily stools at each dose period, although only dose period 3 showed a decrease where the confidence limits did not include 0. At dose period 3 there was a decrease of almost one stool/day. Consistency showed minimal change at each dose period and remained in the soft, formed stool range.

Table 27 Gastrointestinal Function by Dose Period

		Mean number of bowel movements per 24 hours	Mean consistency per bowel movement
Baseline	Mean (SD)	3.1 (2.0)	2.0 (0.4)
	Median (min-max)	3.0 (0.3 to 8.0)	2.0 (1.0 to 2.7)
	Not reported	1	1
Period 1: 0.030 mg/kg/day	Mean (SD)	2.6 (1.3)	2.1 (0.4)
	Median (min-max)	2.3 (0.7 to 5.0)	2.0 (1.0 to 2.7)
	Not reported	1	1
Period 2: 0.060 mg/kg/day	Mean (SD)	2.7 (1.6)	2.1 (0.4)
	Median (min-max)	2.3 (0.3 to 7.0)	2.0 (1.0 to 3.0)
	Not reported	2	2
Period 3: 0.120 mg/kg/day	Mean (SD)	2.1 (1.5)	2.1 (0.4)
	Median (min-max)	2.0 (0.0 to 5.7)	2.0 (1.0 to 3.0)
	Not reported	3	4
Change from baseline to period 1	Mean (SD)	-0.5 (1.5)	0.1 (0.4)
	Median (min-max)	-0.2 (-3.7 to 1.7)	0.0 (-0.3 to 1.4)
	H-L (95% c.i.)*	-0.3 (-1.3, 0.3)	0.0 (-0.1, 0.2)
	Not reported	1	1
Change from baseline to period 2	Mean (SD)	-0.5 (1.2)	0.2 (0.6)
	Median (min-max)	-0.3 (-3.3 to 1.3)	0.1 (-0.9 to 1.0)
	H-L (95% c.i.)*	-0.3 (-1.2, 0.2)	0.2 (-0.1, 0.5)
	Not reported	2	2
Change from baseline to period 3	Mean (SD)	-0.9 (1.2)	0.1 (0.5)
	Median (min-max)	-0.7 (-4.0 to 1.3)	0.0 (-1.0 to 1.0)
	H-L (95% c.i.)*	-0.8 (-1.5, -0.2)	0.1 (-0.1, 0.4)
	Not reported	3	4

Source: Table T50.
*95% C.I.=95% non-parametric confidence interval for Hodges-Lehmann estimate.
Note: Consistency: 1=liquid, 2=soft formed stool, 3=firm hard stool. "Not reported" includes withdrawn patients, missing visits and visits with no recordings of this variable.
H-L=Hodges-Lehmann estimate; Max=maximum; min=minimum; SD=standard deviation.

Source: Table 18, *5.3.4.2.1, p 84*

10.9 Reviewer's Assessment of Safety and Efficacy

In Study 001, administration of tolterodine syrup for 12 weeks for the treatment of detrusor hyperreflexia was generally demonstrated to be safe in 19 pediatric patients with neurogenic lower urinary tract dysfunction, aged 3 months to four years of age. The single event of concern to the reviewer was elevation of AST in one subject, confounded by a minimally increased AST at baseline.

Conclusions about efficacy in this population are compromised by methodological limitations of the study. First, the study is uncontrolled (i.e., there is no placebo group) and non-randomized. There is a large amount of missing data, particularly the urodynamic assessments, which makes interpretation difficult. Even accepting these limitations, the efficacy data do not provide clear evidence of a benefit to the use of tolterodine.

Reviewing the urodynamic data, dose-response trends are noted in only 3 of 9 variables assessed. However, the results are not significant at all dose levels (i.e., the 95% confidence limits around the change from baseline do not include 0) in any of the three variables. Volume to first detrusor contraction shows a significant increase over baseline only at the highest dose, although there is an apparent dose-related increase that does not reach statistical significance at the two lower doses. Intravesical volume at 30 cm H_20 and bladder wall compliance at 0-30 cm display non-significant dose-related increases at each dose level. Bladder wall compliance at 0-20 cm H_20 is significantly increased at only the two higher doses, but not in a dose-response pattern. Looking at the individual urodynamic data for functional bladder capacity, which would perhaps be the most easily interpretable urodynamic parameter that would be expected to improve under treatment (and one with minimal missing values), 10 of 17 subjects with data at all dose levels showed improved values on treatment as compared to baseline, but only 4 of 17 demonstrated a dose-response relationship (and even among these 4, one did not follow the dose-response trend at one dose period).

The patient diary data showed a dose-related reduction in the number of daily incontinence episodes and the mean volume per void, although reductions were significant only at the two higher doses. The mean number of daily catheterizations or micturitions was unchanged. Reviewing individual data, 11 of the 18 patients with data for number of incontinence episodes had improvement over baseline while on treatment, although two of them were worse than baseline at one of the dose levels. Nine of the 18 showed a dose-response trend, although again, four of them did not follow the trend at one of the dose periods. For the mean volume measurement, 13 of 17 subjects with full data had increased volume per void, although four were below baseline on one of the dose levels. Dose-response trends were seen in 12 of 17 subjects, with two of them failing to follow the trend at one dose level. It should be noted that these two measures are not independent: if the number of times the bladder is emptied, whether by micturition, catheterization or incontinence, decreases, the volume per void must increase, unless it is postulated that the medication decreases urinary output.

No clear relationship between drug exposure (by mg/kg) and urodynamic or patient diary results were identified. This apparent lack of an association between exposure and efficacy in pediatric patients with neurogenic lower urinary tract dysfunction for the treatment of detrusor hyperreflexia makes it difficult to determine an optimal dosing regimen.

11 CLINICAL TRIAL 583E-URO-0581-002

11.1 Summary

Title: "Phase I/II, open label, dose escalating, pharmacokinetic, pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine oral solution in children with detrusor hyperreflexia 5 to 10 years of age," dated July 28, 2003, with Amendments dated August 24, 2001 and September 27, 2001.

Amendment #1 was dated August 24, 2001, and included the following changes:

- Added health economics assessments to the study
- Included a phone call from each study site at Visits 3 and 4 to approve the patient's dose escalation
- Clarified Informed Consent items including specifying the risk of "uterine exposure," the volume of blood drawn for PK sampling and deleting reference to the genomics blood draw.

Amendment #2 was dated September 27, 2001, and included the following changes:

- Replaced Appendix 6 to allow saline locks for blood sampling when appropriate
- Clarified Informed Consent items including the dose escalation process at Visits 3 and 4 and data to be collected for the health economics assessment.

First patient enrolled: November 28, 2001

Last patient completed: January 20, 2003

Last follow-up: January 9, 2003 (for patients not continuing in the extension study)

11.2 Objectives

The primary objective was to collect data on which to base dosing recommendations for the use of tolterodine in children five to ten years of age with neurogenic bladder dysfunction, by comparing PK data on the active moiety with data obtained in adults and in children aged 5 to 10 years.

The secondary objectives were to estimate PK variables for tolterodine and DD 01 and to evaluate the PD (urodynamic) and clinical effects, and safety of tolterodine oral solution in patients aged 5 to 10 with neurogenic bladder dysfunction. The tolterodine dose-effect (urodynamic) and the active moiety concentration-effect (urodynamic) relationships were to be determined. An estimate of the direct costs of detrusor hyperreflexia was to be made through the collection of health care utilization data.

11.3 Overall Design

This Phase 1/2, multicenter, 12-week treatment duration, open label, dose escalation, PK, PD, clinical effect and safety study evaluated the use of tolterodine tartrate oral solution in 15 pediatric subjects aged 5 to 10 years for the treatment of detrusor hyperreflexia due to neurogenic conditions. Fourteen U.S. centers were eligible to enroll subjects, with a goal of enrolling 15 subjects total (50% to be 5 to 7 years old, and 50% to be aged 8 to 10 years). Six centers actually enrolled a total of 15 patients, all of whom had sufficient data for the PK analyses. Subjects were enrolled within 3 months of a baseline urodynamic evaluation. Dosing was initiated at 0.03 mg/kg/day in two divided daily doses, which was maintained for four weeks. Following review of safety data, the dose was advanced to 0.06 mg/kg/day for four weeks and then to 0.12 mg/kg/day for four weeks. Urodynamic data, patient diary data, safety data and health care utilization data were collected at the end of each dose period. PK data were collected only at the 0.06 mg/kg/day dose level.

11.4 Study Procedures and Conduct

11.4.1 Schedule of Study Assessments

During the Screening/Baseline Visit (Visit 1), parental informed consent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after medical history, review of systems, physical examination, vital signs, EKG, urinalysis, serum chemistry profile and hematology labs were obtained. The parents were instructed in filling out the patient diary, to be done for the three days preceding entry into the study, once subjects had discontinued excluded drugs for a minimum of 3 days. Subjects who had not had urodynamic testing in the three months prior to study enrollment underwent this procedure at the time of screening. All patients returned to the clinic for study assessments according to the schedule presented in Table 28.

Blood samples for pharmacokinetic analysis were to be collected after completion of the four week 0.06 mg/kg/day dose period, after a total of 8 weeks of treatment. Urodynamic measurements and patient diary completion were to be performed at baseline (at the end of the washout period) and repeated at the end of each four-week dose period (two hours after receiving the last morning dose of that dose level). Any subject who withdrew prior to completion of a dosing level was encouraged to complete the patient diary and evaluation before stopping the medication.

Any subject who developed a clinical UTI during treatment was treated with an appropriate antibiotic for 7 days. Urodynamic testing and patient diary completion were postponed until 3 days after the completion of antibiotic treatment; patients were maintained on their current dose level for up to two additional weeks in cases of delayed urodynamic testing.

Table 28 Study 583E-URO-0581-002 Schedule of Study Assessments

	Visit Number (day)/ Visit Description					
Activity	1 (Day -6 to -14) Screen-ing	2 (Day 1) Baseline	3 (Day 28) 4 weeks	4 (Day 58) 8 weeks (PK visit)	5 (Day 84) 12 weeks	6 (Day 91)* 13 weeks
Informed consent	X					
Medical history	X					
Review of systems and physical examination	X	X	X	X	X	
Inclusion/exclusion criteria	X					
Demographic data	X					
Chemistry and hematology	X		X	X	X	
Urinalysis	X	X	X	X	X	
Dispense patient diary	X	X	X	X		
Return completed diary		X	X	X	X	
Urodynamic testing	X	X	X	X	X	
Adverse events			X	X	X	X
Tolterodine intake†		X	X	X	X	
Blood sample for AGP‡				X		
Blood sample for PK§				X		
Blood sample for genotyping¶			X			
Pregnancy test#	X					
ECG&	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	
Weight	X	X	X	X		
Health care utilization			X	X	X	X

* Phone call 1 week after discharge and, in the case of unresolved AEs, contact 2 weeks after last dose.
† Study medication given to patient to begin intake on the following day. Tolterodine oral solution doses of 0.030 (first 4 weeks), 0.060 (second 4 weeks), and 0.120 mg/kg/day (third 4 weeks) to be administered in divided doses (at approximately 8 AM and 8 PM) from Day 1 to 84.
‡ Sample collected in connection with the blood sample for measuring tolterodine and DD 01.
§ PK samples collected pre-dose and at 0.5, 1, 2, 6 and 8 hours after receiving the 0.030 mg/kg morning dose (at the 0.060 mg/kg/day dosage level).
¶ Sample collected at same time as that taken for chemistry and hematology.
# Menstruating female patients only.
& One ECG at screening, one ECG every 15 minutes for 1 hour (4 total) at Visits 2, 3, and 5, and one ECG coincident with each blood draw at Visit 4 (6 total).
AGP=α1-acid glycoprotein; ECG=electrocardiogram; PK=pharmacokinetics.

Source: Table 1, *5.3.4.2.2, p27*

11.4.2 Study Drug

11.4.2.1 Dose Selection

The drug studied was an investigational product, tolterodine tartrate oral solution, 1 mg/5 ml, which is not commercially available. Three escalating doses (0.03 mg/kg/day, 0.06 mg/kg/day and 0.12 mg/kg/day) were given to all subjects at four week intervals. The mid-range dose was chosen to approximate the exposure of adults receiving 2 mg BID of the tolterodine IR tablet, bracketed by 0.5 and 2 times this dose to explore the dose-response relationship. Dosing was BID, at approximately 8 am and 8 pm. Dose at the second level was determined based on weight obtained at Visit 3.

11.4.2.2 Choice of Comparator

This was an open-label trial; there was no placebo or comparator.

11.4.2.3 Assignment to Study Drug

There was no randomization in this study; all subjects received all doses sequentially.

11.5 Patient Population

11.5.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1) Male or female 5 to 10 years of age, inclusive.
2) Stable neurological disease (meningomyelocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management of urinary drainage.
3) Body weight or body mass index (BMI) within normal range (between the 5^{th} and 95^{th} percentiles), according to the CDC Growth and BMI Charts for the United Sates.
4) Physiologically normal, apart from the stable neurological disease, with no acute illnesses on the basis of the pre-study physical exam.
5) Use of an adequate contraceptive method (including abstinence) during the 3 months prior to inclusion and during study participation for female patients of childbearing potential. Menstruating females were also required to have a negative urine pregnancy test before inclusion.
6) Signed informed parental/guardian consent, with signed informed assent by the patient as appropriate.

Exclusion Criteria

1) Any condition which, in the investigator's opinion, made the patient unsuitable for inclusion.
2) Recent history of clinically significant cardiovascular, hepatic, renal, gastrointestinal or hematological disease, or psychiatric disorder.
3) Suspicion of psychological component of patient's micturition/incontinence problems.
4) Known anatomic abnormalities in the urinary tract, with the exception of vesicoureteral reflux <=grade III.
5) History of management with an indwelling urinary catheter for > 6 months or within 4 weeks of participation in the study.
6) Clinically significant urinary tract infection during the four weeks preceding participation in the study.
7) Any condition contraindicating anticholinergic therapy.

8) Known hypersensitivity to tolterodine or its excipients or history of severe adverse drug reaction to anticholinergic drugs.

9) Treatment with other drugs with significant anticholinergic properties deemed by the investigator to have significant effects on the lower urinary tract, or treatment with drugs affecting bladder function up to 3 days before start of baseline study measurements, or treatment with potent CYP3A4 inhibitors up to 7 days before the start of any pre-study measurements.

10) History of clinically significant hypersensitivity or severe allergy.

11) Patient or parent/guardian unable to understand or cooperate with given information.

12) Participation in a clinical study within 1 month preceding participation in this study or previous participation in this study.

11.5.2 Demographics and Baseline Disease Characteristics

Six US sites enrolled between 1 and 5 patients each, for a total of 15 subjects. Baseline demographic characteristics are summarized in Table 29. The trial included 7 males and 8 females. The majority of the patients (>70%) in the trial were Caucasian. The age breakdown is: 7 subjects between 5 and 7 years, inclusive, and 8 between 8 and 10 years, inclusive. Nine subjects had myelomeningocele; two had a spinal cord injury and six are listed as having a congenital spinal cord anomaly, NOS. Four subjects had vesicoureteral reflux, only one of which was in Grade IV-V. Thirteen subjects were extensive metabolizers, one intermediate and one poor. The median weight was 23.7 kg, ranging from 15.7 to 46.7 kg.

Table 29 Study 583E-URO-0581-002 Baseline Demographics

Demographic Characteristic		Safety/PK Populations N=15
Sex	Male, n (%)	7 (46.7)
	Female, n (%)	8 (53.3)
Age (yrs)	Mean (SD)	7.8 (1.7)
	Median (min, max)	8.0 (5.4, 10.8)
	Not reported	0
Age group	5 to < 8 years, n (%)	7 (46.7)
	8 to < 11 years, n (%)	8 (53.3)
Race	White, n (%)	11 (73.3)
	Black, n (%)	4 (26.7)
Genotype	Extensive metabolizer, n (%)	13 (86.7)
	Intermediate metabolizer, n (%)	1 (6.7)
	Poor metabolizer, n (%)	1 (6.7)

Source: Table T5.
Note: For Patients 203 and 206, the results of genotyping were missing, but the patients are classified as extensive metabolizers based on the bioanalytical results. Age is defined as age at screening (visit 1). Percentage (%) is based on the total number of patients in each population.
Max=maximum; min=minimum; SD=standard deviation.

Source: Table 4, *5.3.4.2.2, p 52*

Medical reviewer comment:

It is not possible to determine the etiology of the neurogenic bladder in all subjects due to the presentation of the medical history data. Categories presented in Study Report Table T12 are non-exclusive, and the individual medical history data is not presented in a systematic way, as it was in Study 001 (e.g. myelomeningocele: yes/no).

11.5.3 Withdrawals, compliance, and protocol violations

No patients discontinued early.

There were two minor violations in inclusion criteria:

- Patient 210 had BMI < 5th percentile
- Patient 216 had BMI > 95th percentile

There were seven major protocol violations in study conduct:

- Patient 204 received a dose double that specified on the PK day. This patient's data was excluded from the PK analysis.
- Patient 216 received a dose half that specified on the PK day. This patient's data was excluded from the PK analysis.

- Patients 205 and 215 reported taking no medication during the diary recording days for the 0.12 mg/kg/day dose. These two patients' data were excluded at this dose period.
- Patient 206 had medication compliance <75% at the PK visit. This patient's data was included in the PK statistics, although diary and urodynamic data was excluded at this dose period.
- Patient 210 received the 0.12 mg/kg/day dose for only 9 days, and Patient 211 received the 0.06 mg/kg/day dose for only 14 days, rather than for the specified 28 days. Both patients' data were included.

Minor deviations included:

- Patient 203 received the 0.12 mg/kg/day dose for 57 days. Patient 210 received the 0.06 mg/kg/day dose for 48 days. Patient 205 received the 0.12 mg/kg/day dose for 17 days. These patients' data were included in the PK statistics.
- Patients 204 and 207's PK samples were received thawed by the lab. Stability studies demonstrated stability of tolterodine and DD 01 in thawed samples for up to seven days. These patients' data were included in the PK statistics.
- Patient 209's urodynamic data at the first dose period was not retrievable.

Compliance was assessed by recording in the patient diary the dates and times of the doses for the three days prior to Visits 3, 4 and 5. Additionally, the bottles of tolterodine were returned at the end of each four-week dosing period, and the amount used was measured and compared to the expected use. Compliance was defined as actual use >75% expected use. There was one patient (206) documented as having poor medication compliance.

Medical reviewer comments:

1) **Individual data on treatment compliance is not provided in the study report.**
2) **Although it is not clearly specified, it appears that dosing at a given level for less than 15 days is considered a major deviation from protocol, while dosing for >14 days but < 28 days is considered a minor deviation. Dosing for more than 28 days also appears to be classified as a minor deviation.**
3) **The rationale for including the pharmacokinetic data but not the clinical effect data for patient 206, who had poor compliance at the PK visit, is unclear.**

11.6 Efficacy

11.6.1 Key Efficacy Endpoints

Clinical effect endpoints included both data obtained by urodynamic evaluation and data derived from patient diaries. The urodynamic variables were:

- volume to first detrusor contraction of >10 cm H_2O pressure,
- functional bladder capacity and leak point pressure,
- intravesical volume at 20 and 30 cm H_2O pressure,
- maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure),
- bladder compliance and
- percent change in cystometric capacity

Dose-PD effects for tolterodine were determined by assessing the urodynamic parameters at each of the three dose levels; concentration-PD effects for the active moiety were determined by assessing the

urodynamic parameters at the PK dose (0.06 mg/kg/day). The urodynamic variables were characterized by descriptive statistics, change from baseline and percent change from baseline at weeks 4, 8 and 12. Three of the urodynamic variables were normalized in relation to each patient's theoretical bladder capacity (calculated by [(2 + age in years) x 30 ml]): volume to first detrusor contraction, functional bladder capacity and intravesical volumes.

The patient diary variables were:

- mean number of catheterizations or micturitions per 24 hours,
- mean volume per catheterization/micturition and
- mean number of incontinence episodes per 24 hours, with the incontinence episodes further classified as to severity on a four point scale

and were based on means derived from three-day diary recordings done at baseline and at each dose period (weeks 4, 8 and 12).

Pharmacokinetic endpoints were the serum PK variables of the active moiety, including AUC_{0-12}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12}, F_{ext}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints.

11.6.2 Primary Efficacy Endpoint Analysis

As in Study 001, clinical effect endpoints were obtained both by urodynamic assessment and by patient diaries, resulting in the same variables. Again, some urodynamic variables were frequently unobtainable due to patient discomfort. Table 30 presents the baseline urodynamic variables and the mean change from baseline at each of the three dose periods. Volume to first detrusor contraction increased in a dose-response manner across all three dose levels, as did intravesical volume and bladder wall compliance at 20 cm H_2O, although only the two higher doses did not include 0 in the confidence intervals around the change from baseline. Intravesical volume and bladder wall compliance at 30 cm H_2O both showed change from baseline at the lowest dose period; the magnitude of this change was similar to that seen at the third dose period and greater than that seen at the 0.06 mg/kg/day dose, although the confidence intervals around the change at the second and third dose periods contained zero. Again, there was no relationship between AUC_{0-12} of the active moiety and change from baseline in the urodynamic variables.

Table 30 Study 002 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	38.4 (40.7)	119.7 (57.4)	45.6 (12.8)	58 (59.2)	81.3 (69.3)	88.7 (66.4)	2.9 (3.0)	2.7 (2.3)	2.2 (1.7)
	N	14	15	12	13	10	6	13	10	6
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	**26.7 (40.3)**	37.2 (69.8)	0 (8.4)	26.9 (73.8)	**65.3 (44.4)**	21.8 (31.7)	1.3 (3.7)	**2.2 (1.5)**	0.5 (0.8)
	N	**11**	14	10	11	7	4	11	7	4
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	**29.6 (42.3)**	40.7 (82.0)	13.3 (28.6)	**35.2 (38.2)**	33.9 (41.6)	49 (120.0)	**1.8 (1.9)**	1.1 (1.4)	1.2 (3.0)
	N	**12**	14	8	**10**	8	4	**10**	8	4
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**37.0 (55.9)**	65.0 (101.0)	2.6 (17.6)	**38.3 (83.6)**	53.1 (90.6)	86.2 (94.4)	**1.9 (4.2)**	1.8 (3.0)	2.2 (2.4)
	N	12	13	8	12	9	6	12	9	6

VFDC= Volume to first detrusor contraction > 10 cm H_2O
FBC = Functional bladder capacity
LPP = Leak point pressure
IVV= Intravesical volume
BWC= Bladder wall compliance
Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Tables 10-12, *5.3.4.2.2, pp 63-65*

Patient diary data, shown in Table 31, was similar to that seen in Study 001. There was again no change in the number of daily catheterizations/micturitions. Dose-related improvements in mean daily incontinence episodes were seen at all three doses, in a dose-response manner. There was an increase in mean volume per catheterization/micturition, although the confidence levels included 0 at all dose periods. There was no relationship between AUC_{0-12} of the active moiety and change from baseline in any of the diary variables.

Table 31 Study 002 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	4.7 (1.4)	4.3 (1.0)	88.8 (45.9)
	N	15	14	15
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	0 (0.8)	**-0.6** **(0.8)**	7.8 (25.7)
	N	15	14	15
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.1** **(1.3)**	6.2 (25.3)
	N	14	13	14
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.3** **(1.3)**	18.9 (30.7)
	N	13	13	13

Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Table 13, *5.3.4.2.2, p 69*

11.7 Pharmacokinetic Assessments

Pharmacokinetic endpoints were the serum PK of the active moiety, including AUC_{0-12}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12}, F_{ext}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints. Samples were taken at visit 4, at the end of the 0.06 mg/kg/day dose period and were obtained pre-dose, and at 0.5, 1, 2, 6 and 8 hours post dose.

11.7.1 Pharmacokinetic Data Summary (PK Population)

Table 32 shows the distribution of the total daily dose of tolterodine in the Study 002 subjects. The mean daily dose at the PK dose level was 1.66 mg/day.

Table 32 Total Daily Dose by Dose Period and Age Group

	Period 1 0.030 mg/kg/day (N=15)		Period 2 0.060 mg/kg/day (N=15)		Period 3 0.120 mg/kg/day (N=15)	
Total Daily Dose in mg:	5 to <8 years	8 to <11 years	5 to <8 years	8 to <11 years	5 to <8 years	8 to <11 years
0.2-0.5 mg	1	1	.	.	.	.
>0.5-1.0 mg	6	5	1	.	.	.
>1.0-2.0 mg	.	2	6	6	1	.
>2.0-3.0 mg	.	.	.	2	4	2
>3.0-4.0 mg	.	.	.	.	2	3
>4.0-5.0 mg	.	.	.	.	.	1
>5.0-6.0 mg	.	.	.	.	.	2
Mean (mg)	0.81		1.66		3.41	
Median (mg)	0.72		1.42		3.06	
Min, Max (mg)	0.49, 1.40		0.95, 2.95		1.92, 6.00	

Source: Table 6, *5.3.4.2.2, p 54*

Pharmacokinetic parameters for the active moiety are displayed in Table 33, and for tolterodine and DD 01 in Table 34.

Table 33 Pharmacokinetic Parameters for the Active Moiety after the 0.03 mg/kg BID dose (0.06 mg/kg/day Regimen) N=13

Parameter	Statistic	Active Moiety
AUC0-12 (nM*hr)	Mean (SD)	7.4 (4.7)
	Median (min, max)	6.3 (4.3, 22.6)
Fext (%)	Mean (SD)	9.9 (5.3)
	Median (min, max)	10.0 (2.4, 19.3)
Cmax (nM)	Mean (SD)	1.78 (1.30)
	Median (min, max)	1.38 (0.79, 5.71)
Cmin (nM)	Mean (SD)	0.10 (0.11)
	Median (min, max)	0.12 (0.00, 0.37)

Source: Table T14b.
Note: Patients 204 and 216 excluded due to incorrect PK dose.
Cmin for all but 2 patients was at time 0; Cmin for two patients (Patients 205 and 210) was at 8 hr.

Source: Table 7, *5.3.4.2.2, p 56*

Table 34 Pharmacokinetic Parameters for Tolterodine and DD 01 after the 0.03 mg/kg BID dose (0.06 mg/kg/day Regimen)

		Tolterodine		DD 01
Parameter	Statistic	Extensive Metabolizer (N=12)	Poor Metabolizer (N=1)	Extensive Metabolizer (N=12)
AUC_{0-12} (µg*hr/L)	Mean (SD)	10.4 (9.3)	50.5	9.1 (7.4)
	Median (min, max)	8.0 (1.5, 35.8)		7.4 (5.0, 32.0)
F_{ext} (%)	Mean (SD)	6.2 (5.1)	16.4	9.9 (5.5)
	Median (min, max)	4.2 (0.6, 16.9)		9.2 (2.7, 20.9)
C_{max} (µg/L)	Mean (SD)	3.28 (2.18)	9.88	2.18 (1.98)
	Median (min, max)	2.48 (0.64, 6.50)		1.50 (0.84, 7.93)
t_{max} (hr)	Mean (SD)	1.01 (0.53)	0.97	1.14 (0.57)
	Median (min, max)	1.00 (0.50, 2.05)		1.00 (0.50, 2.05)
C_{min} (µg/L)	Mean (SD)	0.17 (0.38)	1.62	0.12 (0.13)
	Median (min, max)	0.00 (0.00, 1.34)		0.13 (0.00, 0.41)
$t_{1/2\,z}$ (hr)	Mean (SD)	2.20 (1.00)	3.88	3.01 (1.53)
	Median (min, max)	1.71 (1.05, 4.28)		2.78 (1.56, 7.21)
V_{ss}/F (L)	Mean (SD)	338 (407)	68	NC
	Median (min, max)	126 (66, 1268)		
CL/F (L/hr)	Mean (SD)	107 (128)	12	NC
	Median (min, max)	50 (19, 447)		
V_{ss}/F (L/kg)	Mean (SD)	10.95 (10.12)	2.30	NC
	Median (min, max)	6.54 (3.00, 30.72)		
CL/F (L/hr/kg)	Mean (SD)	3.71 (3.57)	0.41	NC
	Median (min, max)	2.61 (0.55, 13.76)		

Source: Table T14a.
Note: Patients 204 and 216 excluded due to incorrect PK dose. For tolterodine, Cmin for all but 1 patient was at time 0; Cmin for 1 patient (Patient 210) was at 6 hr. For DD 01, Cmin for all but 2 patients was at time 0; Cmin for 2 patients (Patients 205 and 210) was at 8 hr. The weight at visit 4/week 8 was used to calculate the Vss/F (L/kg) and CL/F (L/hr/kg).

Source: Table 8, *5.3.4.2.2, p 57*

Comparison of AUC_{0-12} and C_{max} for this pediatric population and adults receiving 4 mg of tolterodine IR BID was made by the reviewer and is presented in Table 35.

Table 35 AUC_{0-12} and C_{max} of Tolterodine and the Active Moiety in Pediatric Patients and Adults on Tolterodine IR (all extensive metabolizers)

Parameter	Peds 5-10 years 0.03 mg/kg/BID syrup Mean dose 1.7 mg/day	Peds 5-10 years (Study 044) 0.5 mg BID (1 mg/day)	 1 mg BID (2 mg/day)	Adults (healthy volunteers) 2 mg BID tablet (4 mg/day)
Tolterodine* AUC_{0-12} ug*hr/L Mean (SD)	10.4 (9.3) (N=12)	11.2 (13.5) (N=9)	14.8 (10.2) (N=10)	N/A
Tolterodine* C_{max} (ug/L) Mean (SD)	3.3 (2.2) (N=12)	3.4 (3.0) (N=9)	4.9 (2.9) (N=10)	N/A
Active Moiety ** AUC_{0-12} ug*hr/L Mean (SD)	7.4 (4.7) (N=13)	7.2 (2.4) (N=10)	13.9 (4.9) (N=10)	14 (6.4) – 15 (4.3) (Two studies, N = 24 and 18, respectively)
Active Moiety ** C_{max} (ug/L) Mean (SD)	1.8 (1.3) (N=13)	1.8 (0.8) (N=10)	3.9 (1.4) (N=10)	2.8 (0.8) – 3.4 (1.7) (Two studies, N = 18 and 24, respectively)

* Extensive metabolizers only

** Extensive and poor metabolizers

Source: Tables 7 & 8, *5.3.4.2.2, pp 56, 57*, Tables 10.3.4.1.2 and 10.3.4.1.3, *5.3.3.2.3, p 51* and Detrol IR label

AUC for tolterodine is slightly lower in the current study and formulation than that seen in Study 044, with either the dose slightly below or slightly above that used in Study 002, suggesting lower exposure in the group receiving tolterodine syrup compared to children of the same age receiving the immediate release tablet. However, the AUC for the active moiety and C_{max} for both tolterodine and the active moiety is similar to that noted with the 0.5 mg BID dose in Study 044. Compared to adults receiving a 2.5-fold higher dose, active moiety exposure in Study 002 was about half of that seen in the adults.

Medical reviewer's comment:

Tolterodine PK data for adults on the 4 mg/day of immediate release tablets are not presented in the study report.

11.8 Safety

11.8.1 Safety Measurements

The safety population comprised all subjects who received at least one dose of medication; all 15 enrolled subjects are included. A safety evaluation was performed prior to escalation to the next dose. Adverse events were coded according to the Medical Dictionary for Regulatory Activity (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events, classified as serious or non-serious
- Laboratory evaluations (hematology, clinical chemistries, and urinalysis) at Screening and Visits 3, 4 and 5
- 12-lead ECG at each visit (four ECGs obtained at Visits 2, 3 and 5; six at Visit 4). The four ECGs obtained at dose periods 1 and 3 were measured two hours after dosing; the six taken at dose period 2 were taken at 0, 0.5, 1, 2, 6 and 8 hours after dosing.
- Physical examination and vital signs at each visit
- Gastrointestinal function based on baseline review of systems and patient diary recordings

11.8.2 Serious adverse events

Deaths: there were no deaths.

Premature termination due to adverse events: There were no discontinuations from the study for adverse events.

Serious adverse events: There were no serious adverse events. One patient with a known seizure disorder experienced increased seizure frequency during dose periods 1 and 2; this was not reported to be treatment related.

11.8.3 Frequent adverse events

All subjects but one reported at least one adverse event, with approximately equal frequency at each dose period (N=8 during dose period 1, N=10 during dose period 2, N=8 during dose period 3). The most frequent adverse events were UTIs, constipation, fever, diarrhea and headache. Table 36 presents the adverse events occurring in more than 2 subjects in the safety population. The only adverse events considered to be treatment related were three of the cases of constipation and two cases of headache.

Table 36 Adverse Events Reported by Two or More Patients in the Safety Population

System Organ Class (MedDRA)	Preferred Term (MedDRA)	Number (%) of Patients
Infections and infestations	Urinary tract infection NOS	7 (46.7)
Gastrointestinal disorders	Constipation	3 (20.0)
General disorders and administration site conditions	Pyrexia	3 (20.0)
Gastrointestinal disorders	Diarrhoea NOS	2 (13.3)
Nervous system disorders	Headache NOS	2 (13.3)

Source: Table T42.
Note: For patients reporting the same adverse event on more than one occasion, the event was only counted once. Percentage (%) is based on total number of patients in safety population.
NOS=not otherwise specified.

Source: Table 15, *5.3.4.2.2, p 74*

Anticholinergic adverse events were reported by 4 (27%) of the subjects, with constipation (3 patients) and abdominal pain (1 patient) the most frequently reported events. There were no reports of dry mouth.

Medical Reviewer's comment:

1) **Five of the seven subjects with UTIs developed them in dose periods 2 or 3. The UTIs could be related to the study drug if larger volumes per void on treatment**

resulted in an increased tendency to reflux urine. However, review of individual patient data suggests that this is not occurring; only 2 of the 7 patients had (slightly) increased urinary volume over baseline during the treatment periods at which the UTI occurred. Additionally, these patients were being catheterized multiple times each day, so the reviewer considers the serious adverse event of UTI to be expected and unlikely to be related to the study drug.

2) **No CRFs are reported for Study 002; therefore, no details about the two skin disorders (pigmentation disorder NOS, Subject 208 and dermatitis NOS, Subject 216) cannot be ascertained. However, both subjects are listed as "not recovered" at the end of the study (Subject 208 had onset on day 15 and Subject 216 on day 84).**

11.8.4 Laboratory Values

The serum chemistry, hematology, and urinalysis test results were reviewed. Shifts from baseline in laboratory parameters are displayed in Table 37. No clinically significant changes in the laboratory values were noted.

Table 37 Shifts from Baseline in Laboratory Safety Variables

Laboratory Variable	WEEK 4 (DAY 28)			WEEK 8 (DAY 56)		WEEK 12 (DAY 84)		
	Up	Down	Missing	Up	Down	Up	Down	Missing
Aspartate Aminotransferase (AST/SGOT)	1	.	.	2	.	.	.	.
Bilirubin, Total	.	.	.	1	.	.	.	.
Creatinine	1	1	.	.	.	.	.	.
Erythrocytes (Red Blood Cells, RBC)	.	1	2	.	.	.	.	1
Hemoglobin, mass concentration	1	.	2	.	2	.	1	1
Leukocytes (White Blood Cells, WBC)	.	1	2	.	2	.	.	1
Platelet Count	2	.	2	2	.	1	.	1
Potassium (K)	.	.	1	1	.	.	1	.
Sodium (Na)	.	.	.	.	1	.	.	.
Thyroid-Stimulating Hormone (TSH)	.	.	2	.	.	.	.	1

Source: Table T68, *5.3.4.2.2, p 232*

Medical Reviewer's comments:

1) **Table 31 does not include values that were outside the normal range at baseline and continued in the same direction at dosing.**

2) **An apparent error was evident on review of the individual subjects' laboratory data. Subject 203 was reported to have a hemoglobin value at week 4 of 35.5, reported as a high value. However, review of the subject's hemoglobin trend (12 at baseline and week 8, 12.2 at week 12) suggests that this value is inaccurately recorded or may represent hematocrit.**

3) **Two patients displayed a progressive increase in alkaline phosphatase over dose periods, after starting with elevated values at baseline (Subject 202: 387, 360, 462, 468 and Subject 203: 366, 431, 406 and 455 at baseline, period 1, 2 and 3 respectively, with upper limit of normal equal to 350).**

11.8.5 ECGs

No subjects had ECGs read as abnormal at baseline, although six had a sinus tachycardia. All were considered by the investigator to be within the limits of pediatric normality, allowing the subjects to be included in the trial.

At the treatment visits, sinus tachycardia was seen in increasing numbers of subjects at each dose period (Table 38). Only two subjects never had sinus tachycardia (204, 213). With a few exceptions, once tachycardia was observed, it continued to be noted at all subsequent visits. No sinus bradycardia was noted. Only one finding believed to be clinically relevant was noted – patient 210, who had a heart rate of 144 at dose period 2, one hour post-dosing.

Table 38 ECG Rhythms by Dose Period

	Baseline N=15	Period 1 0.030 mg/kg/day N=15	Period 2 0.060 mg/kg/day N=15	Period 3 0.120 mg/kg/day N=15
Normal Sinus Rhythm	9	9	4	3
Sinus Tachycardia	6	6	11	12
Not reported	0	0	0	0

Source: Table T59, *5.3.4.2.2, p 216*

Abnormal QT findings had been defined a priori as a QT interval exceeding 500 msec on any ECG or a change from baseline QT interval of greater than 60 msec. Mean uncorrected and corrected (Fridericia) QT intervals showed no significant change over dose periods (Table 39).

Table 39 Corrected and Uncorrected QT Intervals by Dose Period

		QT (msec)	QTc Fridericia (msec)	QTc Bazett (msec)
Baseline	Mean (SD)	320.6 (18.0)	369.7 (8.6)	397.5 (14.7)
	Median (min, max)	318.0	368.0	396.0
	Not reported	0	0	0
Period 1: 0.030 mg/kg/day	Mean (SD)	325.0 (18.2)	373.8 (13.5)	401.1 (15.8)
	Median (min, max)	325.3	375.5	403.5
	Not reported	0	0	0
Period 2: 0.060 mg/kg/day	Mean (SD)	313.7 (20.1)	370.2 (13.9)	402.5 (15.1)
	Median (min, max)	314.2	365.8	399.8
	Not reported	0	0	0
Period 3: 0.120 mg/kg/day	Mean (SD)	315.5 (20.8)	374.2 (16.9)	408.1 (20.3)
	Median (min, max)	318.5	376.0	409.8
	Not reported	0	0	0
Change from Baseline to period 1	Mean (SD)	4.4 (19.0)	4.0 (13.5)	3.6 (13.3)
	Median (min, max)	5.5	8.8	3.5
	H-L (95% c.i.)*	4.7 (-6.8, 16.0)	4.3 (-4.1, 11.6)	3.9 (-4.0, 11.9)
	Not reported	0	0	0
Change from Baseline to period 2	Mean (SD)	-6.9 (15.8)	0.5 (12.3)	5.1 (15.6)
	Median (min, max)	-4.7	-1.4	0.2
	H-L (95% c.i.)*	-7.9 (-16.0, 2.4)	-0.2 (-7.5, 7.8)	4.2 (-4.9, 14.8)
	Not reported	0	0	0
Change from Baseline to period 3	Mean (SD)	-5.1 (20.1)	4.5 (13.2)	10.7 (12.9)
	Median (min, max)	-6.0	5.8	10.0
	H-L (95% c.i.)*	-5.5 (-18.3, 7.3)	5.3 (-3.0, 12.5)	12.4 (3.3, 18.3)
	Not reported	0	0	0

Source: Table T54a, *5.3.4.2.2, pp 205-208*

There were only two subjects with QT interval greater than 450 msec, one occurring in period 1 and one in period 2 and this was noted only with the Bazett correction. QT prolongation greater than 30 msec beyond baseline was seen in 3.3 to 15% of ECGs, depending on the dose period and the correction used (Table 40). Changes greater than 30 msec in uncorrected QT occurred in three subjects at dose period 1, and two subjects each in dose periods 2 and 3. The highest change was 41 msec, at dose period 1. Using QTcF, two subjects had an elevation >= 30 msec at each dose period, with a maximum of 43 msec. The QTcB correction resulted in higher frequency of change >= 30 msec, with three subjects showing increases at dose periods 1 and 3, and four at dose period 2, with a maximum increase of 59 msec.

Table 40 Change from Baseline QT Interval by Dose Period

		Period 1 N=15		Period 2 N=15		Period 3 N=15	
		n	%	n	%	n	%
QT	< 30 msec	51	85.0	86	96.6	56	93.3
	>= 30 to <60 msec	9	15.0	3	3.4	4	6.7
QTcF	< 30 msec	57	95.0	84	94.4	58	96.7
	>= 30 to <60 msec	3	5.0	5	5.6	2	3.3
QTcB	< 30 msec	56	93.3	80	89.9	55	91.7
	>= 30 to <60 msec	4	6.7	9	10.1	5	8.3

Note: Ns refer to ECGs, not to subjects.

Source: T65, *5.3.4.2.2, p 228*

Medical Reviewer's comments:

1) Sinus tachycardia in this study was defined as heart rate greater than 100 beats/minute. This is inappropriate in a pediatric population, where mean heart rate ranges from 100-108 beats/minute[5].

2) The criteria for defining a QT interval or interval change as abnormal in this study (>500 msec, >60 msec) are commonly used as thresholds for discontinuation from a trial. The results are reported by the more stringent criteria of interval >= 450 msec and change >= 30 msec. This is appropriate as the upper limit of normal QT interval in children is reported to be 450 msec in males and 460 msec in females (Garson, 1993). The maximal QTcB interval greater than 450 was 457 and occurred on only one of four recordings during dose period 1.

3) The highest proportion of QT interval change from baseline > 30 msec occurred with the Bazett correction, which is known to overcorrect at higher heart rates (i.e., as seen in children).

11.8.6 Vital Signs

Blood pressure, pulse, temperature and respiratory rate were obtained at each visit; however, neither composite nor individual data are reported.

Medical Reviewer's comment:

No data on vital signs evaluations are presented.

11.8.7 Gastrointestinal Function

Gastrointestinal function was assessed at each visit by patient diary reports of number of bowel movements over three days, along with assessment of their consistency. Parents were also asked to comment on the subject's bowel regimen and any changes noted over the four week treatment interval. Table 41 presents the mean number of daily bowel movements and mean consistency over each treatment period. There were fewer daily stools in the three treatment periods, although confidence limits around the change scores all included 0. Consistency showed minimal change at each dose period and remained in the soft, formed stool range.

Table 41 Gastrointestinal Function by Dose Period

		Mean number of bowel movements per 24 hours	Mean consistency per bowel movement
Baseline	Mean (SD)	1.6 (1.2)	2.0 (0.4)
	Median (min, max)	1.3 (0.3, 4.7)	2.0 (1.0, 3.0)
	Not reported	2	2
Period 1: 0.030 mg/kg/day	Mean (SD)	1.0 (0.7)	2.2 (0.4)
	Median (min, max)	1.0 (0.3, 2.7)	2.0 (1.5, 3.0)
	Not reported	2	2
Period 2: 0.060 mg/kg/day	Mean (SD)	1.3 (1.1)	2.2 (0.4)
	Median (min, max)	1.2 (0.3, 3.3)	2.0 (1.5, 3.0)
	Not reported	3	3
Period 3: 0.120 mg/kg/day	Mean (SD)	1.3 (1.1)	2.0 (0.6)
	Median (min, max)	1.0 (0.3, 4.3)	2.0 (1.0, 3.0)
	Not reported	2	2
Change from baseline to period 1	Mean (SD)	-0.6 (0.7)	0.2 (0.4)
	Median (min, max)	-0.3 (-2.0, 0.3)	0.0 (-0.3, 1.0)
	H-L (95% C.I.)*	-0.5 (-1.0, 0.0)	0.1 (0.0, 0.5)
	Not reported	2	2
Change from baseline to period 2	Mean (SD)	-0.3 (1.1)	0.2 (0.4)
	Median (min, max)	-0.3 (-2.7, 1.3)	0.0 (-0.5, 1.0)
	H-L (95% C.I.)*	-0.3 (-1.0, 0.3)	0.1 (-0.1, 0.5)
	Not reported	3	3
Change from baseline to period 3	Mean (SD)	-0.3 (1.0)	0.0 (0.7)
	Median (min, max)	-0.3 (-2.7, 0.7)	0.0 (-1.1, 1.0)
	H-L (95% C.I.)*	-0.2 (-1.0, 0.3)	0.0 (-0.5, 0.5)
	Not reported	2	2

Source: Table T50.
*95% C.I.=95% non-parametric confidence interval for Hodges-Lehman estimate.
Note: Consistency: 1=liquid, 2=soft formed stool, 3=firm hard stool. "Not reported" includes missing visits and visits with no recordings of this variable.
H-L=Hodges-Lehman estimate, Max=maximum; min=minimum; SD=standard deviation.

Source: Table 18, *5.3.4.2.2, p 81*

11.9 Reviewer's assessment of efficacy and safety

In Study 002, administration of tolterodine syrup for 12 weeks for the treatment of detrusor hyperreflexia was demonstrated to be generally safe in 15 pediatric patients with neurogenic lower urinary tract dysfunction, aged 5 to 10 years of age. There was noted to be one exacerbation of a seizure disorder, and a greater occurrence of UTIs as the trial progressed, although the effects of time and increased tolterodine dose cannot be separated. No new and unlabeled safety issues were identified.

Determination of efficacy in this population is compromised by the methodological limitations of the study. First, the study is uncontrolled (i.e., there is no placebo group) and non-randomized. There is a large amount of missing data, particularly on the urodynamic assessments, which makes

interpretation difficult. Even accepting these limitations, the efficacy data do not provide clear evidence of a benefit to use of tolterodine.

Reviewing the urodynamic data, dose-response trends are noted in 6 of 9 variables assessed. However, the trends are not statistically significant in any of the urodynamic variables. Where a statistically significant change from baseline was shown, it did not occur at all doses, or even consistently at the higher doses. Looking at the individual urodynamic data for functional bladder capacity, which would perhaps be the most easily interpretable parameter that would be expected to improve under treatment (and one with no missing values), 12 of 15 subjects showed improved values on treatment as compared to baseline, but only 8 of 15 demonstrated a dose-response relationship (and even among these 8, four did not follow the dose-response trend at one dose period).

Similarly, the patient diary data showed a statistically significant dose-related reduction only in the number of daily incontinence episodes. The mean number of daily catheterizations or micturitions was unchanged and the mean volume per void, while apparently increased on treatment, did not change significantly from baseline, and showed no dose-response. Reviewing individual data, 11 of the 14 patients with data for number of incontinence episodes had improvement over baseline while on treatment, although four of them were worse than baseline at one of the dose levels. Nine of the 14 showed a dose-response trend, although again, four of them failed to do so at one of the dose periods.

No clear relationship between drug exposure (by mg/kg) and urodynamic or patient diary results were identified. This apparent lack of an association between exposure and efficacy in pediatric patients with neurogenic lower urinary tract dysfunction for the treatment of detrusor hyperreflexia makes it difficult to assess efficacy and/or determine an optimal dosing regimen.

12 CLINICAL TRIAL 583E-URO-0581-003

12.1 Summary

Title: "Phase I/II, open label, dose escalating, pharmacokinetic, pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine PR capsules in children with detrusor hyperreflexia 11 to 15 years of age," dated August 4, 2003, with Amendments dated August 24, 2001 and September 27, 2001.

Amendment #1 was dated August 24, 2001, and included the following changes:

- Added health economics assessments to the study
- Included a phone call from each study site at Visits 3 and 4 to approve the patient's dose escalation
- Clarified Informed Consent items including specifying the risk of "uterine exposure," the volume of blood drawn for PK sampling and deleting reference to the genomics blood draw.
- Eliminated the use of catheters for PK specimen collection

Amendment #2 was dated September 27, 2001, and included the following changes:

- Replaced Appendix 6 to allow saline locks for blood sampling when appropriate
- Clarified Informed Consent items including the dose escalation process at Visits 3 and 4 and data to be collected for the health economics assessment.

First patient enrolled: March 19, 2002

Last patient completed: May 21, 2003

Last follow-up: June 11, 2003

12.2 Objectives

The primary objective was to collect data on which to base dosing recommendations for the use of tolterodine in children eleven to fifteen years of age with neurogenic bladder dysfunction, by comparing PK data on the active moiety with data obtained in adults and in children aged 5 to 15 years.

The secondary objectives were to estimate PK variables for tolterodine and DD 01 and to evaluate the PD (urodynamic) and clinical effects, and safety of tolterodine prolonged release (PR) capsules in patients aged 11 to 15 with neurogenic bladder dysfunction. The tolterodine dose-effect (urodynamic) and the active moiety concentration-effect (urodynamic) relationships were to be determined. An estimate of the direct costs of detrusor hyperreflexia was to be made through the collection of health care utilization data.

12.3 Overall Design

This Phase 1/2, multicenter, 12-week treatment duration, open label, dose escalation, PK, PD, clinical effect and safety study evaluated the use of tolterodine PR capsules in 11 pediatric subjects aged 11 to 15 years for the treatment of detrusor hyperreflexia due to neurogenic conditions. Fourteen U.S. centers were eligible to enroll subjects, with a goal of enrolling 15 subjects total (60% to be 11 to 13 years old, and 40% to be aged 14 to 15 years). Six centers actually enrolled a total of 11 patients, ten of whom had sufficient data for the PK analyses. Subjects were enrolled within 3 months of a baseline urodynamic evaluation. Dosing was initiated at 2 mg/day, which was maintained for four weeks. Following review of safety data, the dose was advanced to 4 mg/day for four weeks and then to 6 mg/day for four weeks. Urodynamic data, patient diary data, safety data and health care utilization data were collected at the end of each dose period. PK data were collected only at the 4 mg/day dose level.

12.4 Study Procedures and Conduct

12.4.1 Schedule of Study Assessments

During the Screening/Baseline Visit (Visit 1), parental informed consent and subject informed assent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after medical history, review of systems, physical examination, vital signs, EKG, urinalysis, serum chemistry profile and hematology labs were obtained. The parents were instructed in filling out the patient diary, to be done for the three days preceding entry into the study, once subjects had discontinued excluded drugs for a minimum of 3 days. Subjects who had not had urodynamic testing in the three months prior to study enrollment underwent this procedure at the time of screening. All patients returned to the clinic for study assessments according to the schedule presented in Table 42.

Blood samples for pharmacokinetic analysis were to be collected after completion of the four week 4 mg/day dose period, after a total of 8 weeks of treatment. Urodynamic measurements and patient diary completion were to be performed at baseline (at the end of the washout period) and repeated at the end of each four-week dose period (two hours after receiving the last morning dose of that dose level). Any subject who withdrew prior to completion of a dosing level was encouraged to complete the patient diary and evaluation before stopping the medication.

Any subject who developed a clinical UTI during treatment was treated with an appropriate antibiotic for 7 days. Urodynamic testing and patient diary completion were postponed until 3 days after the completion of antibiotic treatment; patients were maintained on their current dose level for up to two additional weeks in cases of delayed urodynamic testing.

Table 42 Study 583E-URO-0581-003 Schedule of Study Assessments

Activity	Visit Number (day)/ Visit Description					
	1 (Day -6 to Day -14)	2 (Day 1)	3 (Day 28)	4 (Day 58)	5 (Day 84)	6 (Day 91)*
	Screen-ing	Baseline	4 weeks	8 weeks (PK visit)	12 weeks	13 weeks
Informed consent	X					
Medical history	X					
Review of systems and physical examination	X	X	X	X	X	
Inclusion/exclusion criteria	X					
Demographic data	X					
Chemistry and hematology	X		X	X	X	
Urinalysis	X	X	X	X	X	
Dispense patient diary	X	X	X	X		
Return completed diary		X	X	X	X	
Urodynamic testing	X	X	X	X	X	
Adverse events			X	X	X	X
Tolterodine intake†		X	X	X	X	
Blood sample for AGP‡				X		
Blood sample for PK§				X		
Blood sample for genotyping¶			X			
Pregnancy test#	X					
ECG&	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	
Weight	X	X	X	X		
Health care utilization			X	X	X	X

* Phone call 1 week after discharge and, in the case of unresolved AEs, contact 2 weeks after last dose.
† Study medication given to patient to begin intake on the following day. Tolterodine PR capsules doses of 2- (first 4 weeks), 4- (second 4 weeks), and 6 mg/day (third 4 weeks) to be administered once daily (at approximately 8 AM) from Day 1 to 84.
‡ Sample collected in connection with the blood sample for measuring tolterodine and DD 01.
§ PK samples collection: maximum 10 minutes before dose, 0.5, 1, 3, 4, 6, 12, and 24 hours post-dose on the PK Day visit 4 after receiving the 4 mg/day dose regimen.
¶ Sample collected at same time as that taken for chemistry and hematology.
# Menstruating female patients only.
& One ECG at screening, one ECG every 15 minutes for 1 hour (4 total) at Visits 2, 3, and 5, and one ECG coincident with each blood draw at Visit 4 (8 total).
AGP=α_1-acid glycoprotein; ECG=electrocardiogram; PK=pharmacokinetics.

Source: Table 1, *5.3.4.2.3, p27*

12.4.2 Study Drug

12.4.2.1 Dose Selection

The drug studied was tolterodine tartrate prolonged release (PR), 2 and 4 mg capsules. Three escalating doses (2 mg/day, 4 mg/day and 6 mg/day) were given to all subjects at four week intervals. The mid-range dose was chosen to approximate the exposure of adults receiving 4 mg/day of the tolterodine PR tablet, bracketed by 0.5 and 1.5 times this dose to explore the dose-response relationship. Dosing was once per day, at approximately 8 am. Subjects who were unable to swallow

the capsule were allowed to empty the capsule and consume the beads sprinkled over food. The beads were not to be chewed or crushed.

Medical reviewer comment:

No data are provided regarding the number or identity of subjects who ingested tolterodine in bead form rather than as an intact capsule. The effect of method of administration on pharmacokinetics and pharmacodynamics therefore cannot be determined.

12.4.2.2 Choice of Comparator

This was an open-label trial; there was no placebo or comparator.

12.4.2.3 Assignment to Study Drug

There was no randomization; all patients received all doses of tolterodine in an open-label dose-escalation fashion. The mid-range dose, 4 mg/day was chosen to provide equivalence with adult dosing; doses of one-half and 1.5 times the adult dose were chosen to allow exploration of dose-response effects.

12.5 Patient Population

12.5.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1) Male or female between 11-15 years of age, inclusive.

2) Stable neurological disease (meningomyelocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management of urinary drainage.

3) Body weight or body mass index (BMI) within normal range (between the 5th and 95th percentiles), according to the CDC Growth and BMI Charts for the United Sates.

4) Physiologically normal, apart from the stable neurological disease, with no acute illnesses on the basis of the *pre*-study physical exam

5) Signed informed parental/guardian consent, with signed informed assent by the patient as appropriate.

Exclusion Criteria

1) Any condition which, in the investigator's opinion, made the patient unsuitable for inclusion.

2) Recent history of clinically significant cardiovascular, hepatic, renal, gastrointestinal or hematological disease, or psychiatric disorder.

3) Suspicion of psychological component of patient's micturition/incontinence problems.

4) Known anatomic abnormalities in the urinary tract, with the exception of vesicoureteral reflux <=grade III.

5) History of management with an indwelling urinary catheter for > 6 months or within 4 weeks of participation in the study.

6) Clinically significant urinary tract infection during the four weeks preceding participation in the study.

7) Any condition contraindicating anticholinergic therapy.

8) Known hypersensitivity to tolterodine or its excipients or history of severe adverse drug reaction to anticholinergic drugs.

9) Treatment with other drugs with significant anticholinergic properties deemed by the investigator to have significant effects on the lower urinary tract, or treatment with drugs affecting bladder function up to 3 days before start of baseline study measurements, or treatment with potent CYP3A4 inhibitors up to 7 days before the start of any pre-study measurements.

10) History of clinically significant hypersensitivity or severe allergy.

11) Parent/guardian unable to understand or cooperate with given information.

12) Participation in a clinical study within 1 month preceding participation in this study or previous participation in this study.

12.5.2 Demographics and Baseline Disease Characteristics

Six US sites enrolled between 1 and 4 patients each, for a total of 11 subjects. One patient was unable to have blood drawn and was therefore excluded from the PK analysis (this subject also withdrew from the trial after 63 days). Baseline demographic characteristics are summarized in Table 43. The trial included 5 males and 6 females (five of each in the PK population.) The majority of the patients (>70%) in the trial were Caucasian. The age breakdown is: 8 subjects between 11 and 13 years, inclusive, and 3 between 14 and 15 years, inclusive (8 and 2 respectively, in the PK population). Eight subjects had myelomeningocele and two are listed as having a congenital spinal cord anomaly, NOS. Three subjects had vesicoureteral reflux, all of which were in Grade I-III. Seven (6 in the PK population) subjects were extensive metabolizers, one intermediate and three poor. The median weight was 55.3 kg, ranging from 25.9 to 75.7 kg.

Medical reviewer comments:

1) **The age distribution is different from that specified in the protocol: 40% of an expected 15 subjects, or 6 subjects, were to have been between 14-15 years old. Only two subjects (20% of the actual number enrolled) in this age group are included in the PK population.**
2) **The listing of etiologies of neurogenic bladder dysfunction is incomplete; only 10 subjects are accounted for, and the individual listings of medical history are not presented in a standardized format. Subject 301 is noted to have a spinal cord tumor and transverse myelitis, but it is not clear if this is the subject unaccounted for by either myelomeningocele or other congenital spinal cord anomaly.**

Table 43 Study 583E-URO-0581-003 Baseline Demographics

		Safety Population N=11	PK Population N=10
Sex	Male , n (%)	5 (45.5)	5 (50.0)
	Female, n (%)	6 (54.5)	5 (50.0)
Age(years)	Mean (SD)	13.3 (1.4)	13.1 (1.3)
	Median (min, max)	13.1 (11.5, 15.5)	13.0 (11.5, 15.3)
	Not reported	0	0
Age group	11 to < 14 years, n (%)	8 (72.7)	8 (80.0)
	14 to < 16 years, n (%)	3 (27.3)	2 (20.0)
Race	White, n (%)	8 (72.7)	8 (80.0)
	Black, n (%)	3 (27.3)	2 (20.0)
Genotype	Extensive Metabolizer, n (%)	7 (63.6)	6 (60.0)
	Intermediate Metabolizer, n (%)	1 (9.1)	1 (10.0)
	Poor Metabolizer, n (%)	3 (27.3)	3 (30.0)

Source: Table T5. .
Note: For patients 301, 303, and 314, the results of genotyping were missing, but the patients are classified as EM based on their bioanalytical results
Age is defined as age at screening (visit 1). Percentage (%) is based on the total number of patients in each population.
Max=maximum; min=minimum; SD=standard deviation

Source: Table 4, *5.3.4.2.3, p 50*

12.5.3 Withdrawals, compliance, and protocol violations

One patient (312) withdrew consent after 63 days on treatment.

There were three minor violations in inclusion criteria:

- Patient 307 had BMI < 5th percentile
- Patients 302 and 303 had BMI >95th percentile

There were three major protocol violations in study conduct:

- Patients 312 and 313 had medication compliance <75% at Visit 4. (Patient 312 also did not have PK samples drawn after repeated attempts.) Diary and urodynamic data were excluded at Visit 4 for these patients.

Minor deviations included:

- Patient 302 received the 6 mg dose for only 6 days, then decreased to 4 mg for the remaining 27 days, apparently due to constipation. This patient's data were included for Visit 5.
- Patient 307 stopped the 6 mg dose for 5 days for reasons that are not noted. Although this patient is not listed as noncompliant at Visit 5, the investigator questioned this patient's compliance. Nonetheless, this patient's data were included for Visit 5.
- Patient 305 did not take the 6 mg dose on the day preceding visit 4, and took the 6 mg dose for only 16 days. It is also noted that compliance at visit 5 was "close to 75%." This patient is not listed as non-compliant and the patient's data were included for Visit 5.
- Serum concentrations in patients 301, 305, 309 and 313 were higher at 24 hours than 12 hours post-dose on the PK day, raising the possibility that they had taken an additional dose. Data from these patients were excluded from the PK statistics.

Compliance was assessed by recording in the patient diary the dates and times of the doses for the three days prior to Visits 3, 4 and 5. Additionally, the blister packs of tolterodine PR capsules were returned at the end of each four-week dosing period, and the number used was counted and compared to the expected use. Compliance was defined as actual use >75% expected use. There are at least two and possibly four patients who did not meet criteria for compliance at least one of the study periods.

Medical reviewer comments:

1) **No further information is provided about the patient who withdrew consent for the trial.**
2) **It appears that assessment of compliance is based both on the data in the patient diary and the investigator's calculation of % of expected drug taken. No procedures for resolving discrepancies between these two methods are delineated.**
3) **Individual data on treatment compliance data are not provided in the study report.**
4) **The rationale for including data from period 3 for Subject 302, who was on a lower than expected dose for most of this dose period, and for Subjects 305 and 307, who had less than the full duration of dosing, is not given.**
5) **It does not appear appropriate to the reviewer that data from subjects 301, 305, 309 and 313 was excluded from the PK statistics.**

12.6 Efficacy

12.6.1 Key Efficacy Endpoints

Clinical effect endpoints included both data obtained by urodynamic evaluation and data derived from patient diaries. The urodynamic variables were:

- volume to first detrusor contraction of >10 cm H_2O pressure,
- functional bladder capacity and leak point pressure,
- intravesical volume at 20 and 30 cm H_2O pressure,
- maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure),
- bladder compliance and
- percent change in cystometric capacity

Dose-PD effects for tolterodine were determined by assessing the urodynamic parameters at each of the three dose levels; concentration-PD effects for the active moiety were determined by assessing the urodynamic parameters at the PK dose (4 mg/day). The urodynamic variables were characterized by descriptive statistics, change from baseline and percent change from baseline at weeks 4, 8 and 12. Three of the urodynamic variables were normalized in relation to each patient's theoretical bladder capacity (calculated by [60 + (age in years x 30) ml]): volume to first detrusor contraction, functional bladder capacity and intravesical volumes.

Medical Reviewer's Comment:

The formula used to normalize volumetric data differs from that used in Studies 001 and 002. No citation is provided to justify use of either normalization procedure.

The patient diary variables were:

- mean number of catheterizations or micturitions per 24 hours,
- mean volume per catheterization/micturition and

- mean number of incontinence episodes per 24 hours, with the incontinence episodes further classified as to severity on a four point scale

and were based on means derived from three-day diary recordings done at baseline and over the three days prior to Visits 3, 4 and 5.

Pharmacokinetic endpoints were the serum PK variables of the active moiety, including AUC_{0-24}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-24}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints.

12.6.2 Primary Efficacy Endpoint Analysis

As in Studies 001 and 002, clinical effect endpoints were obtained both by urodynamic assessment and by patient diaries, resulting in the same variables. Again, the same urodynamic variables were frequently unobtainable due to patient discomfort. Table 44 presents the baseline urodynamic variables and the mean change from baseline at each of the three dose periods. There were significant non-dose-related changes from baseline in functional bladder capacity at dose periods 1 and 3, with the increase on the lower dose exceeding that on the maximal dose. Interpretation of data on the intravesical volume and bladder wall compliance variables is hampered by very small sample sizes. Again, there was no relationship between AUC_{0-12} of the active moiety and change from baseline in the urodynamic variables.

Table 44 Study 003 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	132.4 (76.7)	232.0 (62.7)	33.9 (15.1)	150.1 (95.4)	153.6 (47.6)	197.7 (49.0)	7.5 (4.8)	5.1 (1.6)	4.9 (1.2)
	N	11	11	9	9	5	3	9	5	3
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	25.9 (107.6)	**79.1 (90.8)**	2.0 (19.8)	72.8 (104.2)	143.7 (102.9)	134.5 (74.2)	3.6 (5.2)	4.8 (3.4)	3.4 (1.9)
	N	10	11	7	8	3	2	7	3	2
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	35.0 (59.4)	-3.8 (71.8)	5.8 (14.2)	56.0 (82.1)	22.8 (36.6)	-77.0 (28.3)	2.8 (4.1)	0.8 (1.2)	-1.9 (0.7)
	N	8	9	5	7	4	2	7	4	2
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	18.9 (114.4)	**59.4 (67.0)**	-6.4 (19.1)	45.6 (67.9)	**67.8 (61.7)**	54.0 (111.7)	2.3 (3.4)	**2.3 (2.1)**	1.4 (2.8)
	N	8	10	5	7	4	2	7	4	2

VFDC= Volume to first detrusor contraction > 10 cm H_2O
FBC = Functional bladder capacity
LPP = Leak point pressure
IVV= Intravesical volume
BWC= Bladder wall compliance
Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Tables 10-12, *5.3.4.2.3 pp 60-62*

Patient diary data are shown in Table 45. As in the previous two studies, there was no change in the number of daily catheterizations/micturitions. Dose-related improvements in mean daily incontinence episodes were seen at all three doses, although of an equal magnitude at each dose level. Mean volume per void increased significantly over baseline only at the 4 mg/day dose. There was no relationship between AUC_{0-12} of the active moiety and change from baseline in any of the diary variables.

Table 45 Study 003 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	5.4 (1.9)	2.4 (1.8)	131.9 (48.8)
	N	11	11	11
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	-0.3 (0.9)	**-0.6 (0.6)**	38.4 (60.4)
	N	11	**11**	11
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.7 (2.0)	**-0.9 (0.9)**	**34.3 (30.9)**
	N	9	**9**	9
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.9 (2.0)	**-0.7 (0.8)**	38.5 (66.5)
	N	10	10	10

Bold cells – Confidence interval around the change from baseline does not contain 0

Source: Table 13, *5.3.4.2.3, p 66*

12.7 Pharmacokinetic Assessments

Pharmacokinetic endpoints were the serum PK of the active moiety, including AUC_{0-24}, C_{max} and C_{min}. Secondary PK endpoints were calculated for tolterodine and DD 01, including AUC_{0-24}, C_{max}, t_{max}, C_{min} and $t_{1/2}$. The oral steady state volume of distribution Vss/F and the oral serum clearance CL/F for tolterodine were additional secondary endpoints. Samples were taken at visit 4, at the end of the 4 mg/day dose period and were obtained pre-dose, and at 0.5, 1, 3, 4, 6, 12 and 24 hours post dose.

12.7.1 Pharmacokinetic Data Summary (PK Population)

Pharmacokinetic parameters for the active moiety are displayed in Table 46, and for tolterodine and DD 01 in Table 47.

Table 46 Pharmacokinetic Parameters for the Active Moiety after the 4 mg/day dose N=10

Parameter	Statistic	Active Moiety N=10
AUC_{0-24}(nM*hr)	Mean (SD)	27.3 (10.5)
	Median (min, max)	25.5 (11.5, 43.4)
C_{max} (nM)	Mean (SD)	2.10 (0.93)
	Median (min, max)	1.89 (1.03, 3.86)
C_{min} (nM)	Mean (SD)	0.619 (0.272)
	Median (min, max)	0.599 (0.237, 1.233)

Source: Table T14b.
Note: Cmin at time 0.5 except patient 313 Cmin at 0 hr and patients 303 and 306 Cmin at 24 hr

Source: Table 7, *5.3.4.2.3, p 54*

Table 47 Pharmacokinetic Parameters for Tolterodine and DD 01 after the 4 mg/day dose

		Tolterodine		DD 01
Parameter	Statistic	Extensive Metabolizer N=7	Poor Metabolizer N=3	Extensive Metabolizer N=7
AUC_{0-24} (µg*hr/L)	Mean (SD)	48.3 (41.1)	331.5 (19.8)	30.5 (6.0)
	Median (min, max)	31.2 (8.0, 129.8)	326.1 (315.0, 353.5)	32.7 (20.0, 36.9)
C_{max} (µg/L)	Mean (SD)	4.63 (3.01)	18.77 (1.42)	2.58 (0.72)
	Median (min, max)	3.93 (0.69, 8.77)	18.00 (17.90, 20.40)	2.43 (1.80, 3.89)
t_{max}(hr)	Mean (SD)	3.29 (0.49)	3.30 (0.61)	3.86 (1.07)
	Median (min, max)	3.00 (3.00, 4.00)	3.00 (2.90, 4.00)	4.00 (3.00, 6.00)
C_{min} (µg/L)	Mean (SD)	0.980 (0.938)	9.723 (1.973)	0.646 (0.320)
	Median (min, max)	0.677 (0.204, 2.980)	8.650 (8.520, 12.000)	0.572 (0.363, 1.190)
$t_{1/2,z}$(hr)	Mean (SD)	8.86 (4.00)	28.89 (10.72)	11.38 (8.03)
	Median (min, max)	8.53 (3.67, 13.44)	25.74 (20.10, 40.84)	9.46 (3.40, 28.04)
V_{ss}/F(L)	Mean (SD)	1530 (2081)	344 (112)	NC
	Median (min, max)	672 (297, 6129)	323 (243, 465)	
CL/F(L/hr)	Mean (SD)	110 (109)	8 (0)	NC
	Median (min, max)	88 (21, 344)	8 (8, 9)	
V_{ss}/F(L/kg)	Mean (SD)	29.62 (39.38)	5.77 (2.02)	NC
	Median (min, max)	15.94 (7.72, 117.86)	4.78 (4.43, 8.09)	
CL/F (L/hr/kg)	Mean (SD)	2.20 (2.03)	0.14 (0.01)	NC
	Median (min, max)	1.85 (0.40, 6.62)	0 14 (0.13, 0.15)	

Source: Table T14a.
Tolterodine: Cmin at time 0 except patients 302, 305 and 309 Cmin at 0.5 hr, patient 301 Cmin at 12 hr and patients 303, 306 and 311 Cmin at 24 hr
DD 01: Cmin at time 0.5 except patient 313 Cmin at 0 hr and patient 303 Cmin at 24 hr
The weight at visit 4/week 8 was used to calculate the Vss/F (L/kg) and CL/F (L/hr/kg)
For patient 313 weight at visit 4/week 8 was missing so the weight at visit 3/week 4 was used to calculate the Vss/F (L/kg) and CL/F (L/hr/kg)
Patient 307, an intermediate metabolizer, is categorized as an extensive metabolizer
NC=not calculated

Source: Table 8, *5.3.4.2.3, p 55*

As dosing in this study was not weight-based, the relationship of AUC to body weight was examined. There was an apparent decrease in AUC with increasing weight and BMI, although there was a great deal of variability and this trend did not reach statistical significance.

Comparison of active moiety AUC_{0-24} and C_{max} for this pediatric population, other 11-15 year olds being treated for urinary urge incontinence (Study 018) and adults receiving 4 mg of tolterodine PR was made and is presented in Table 48.

Table 48 Comparison of Active Moiety AUC and Cmax in Adolescents and Adults on 4 mg/day Tolterodine PR

Parameter	Statistic	11-15 year old Neurogenic Bladder* N=10	11-15 year old Overactive Bladder [12] N=20	Healthy Adult Subjects [20] N=17
AUC_{0-24}(nM*hr)	Mean (SD)	27.3 (10.5)	29.7 (11.1)	30.4 (13.7)
	Median (min, max)	25.5 (11.5, 43.4)	26.7 (14.4, 52.3)	26 (13, 52)
C_{max} (nM)	Mean (SD)	2.10 (0.93)	2.17 (0.95)	2.3 (1.0)
	Median (min, max)	1.89 (1.03, 3.86)	2.07 (0.93, 5.25)	2.70 (0.77, 3.70)

* Table T14b
Source: Table 14b
PR=Prolonged release; SD=standard deviation

Source: Table 9, *5.3.4.2.3, p 57*

The AUC and Cmax are slightly lower in adolescents than adults receiving the same dose, and the neurogenic population is slightly lower than the adolescents with urinary urge incontinence. No comparison by dose/kg is presented.

12.8 Safety

12.8.1 Safety Measurements

The safety population comprised all subjects who received at least one dose of medication; all 11 enrolled subjects are included. A safety evaluation was performed prior to escalation to the next dose. Adverse events were coded according to the Medical Dictionary for Regulatory Activity (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events, classified as serious or non-serious
- Laboratory evaluations (hematology, clinical chemistries, and urinalysis) at Screening and Visits 3, 4 and 5
- 12-lead ECG at each visit (four ECGs obtained at Visits 2, 3 and 5; six at Visit 4)
- Physical examination and vital signs at each visit
- Gastrointestinal function based on baseline review of systems and patient diary recordings at Visits 2-5

Medical Reviewer's comment:

The schedule for obtaining ECGs notes that at dose period 2, six ECGs were obtained; however, these are described at being taken at eight distinct time periods. It is unclear which six of these time intervals were actually sampled.

12.8.2 Serious adverse events

Deaths: there were no deaths.

Premature termination due to adverse events: there were no terminations due to adverse events.

Serious adverse events: Two serious adverse events occurred in a single patient (erythema and a skin ulcer on the right foot, which had been in a cast prior to study enrollment); both were considered unrelated to the study medication.

Medical Reviewer's comment:

The reviewer agrees that the two SAEs are unlikely to be related to the study medication.

12.8.3 Frequent adverse events

All subjects reported at least one adverse event, with approximately equal frequency at each dose period (N=7 during dose period 1, N=7 during dose period 2, N=6 during dose period 3). The most frequent adverse events were UTI, followed by fever, back pain, headache, dysmenorrheal and pressure sore. Table 49 presents the adverse events occurring more than 2 subjects in the safety population. The only adverse event considered by the investigator to be treatment related was one of the cases of constipation.

Table 49 Adverse Events Reported by Two or More Patients in the Safety Population

System Organ Class (MedDRA)	Preferred term (MedDRA)	Number (%) of patients
Infections and infestations	Urinary tract infection NOS	4 (36.4)
General disorders and administration site conditions	Pyrexia	2 (18.2)
Musculoskeletal, connective tissue and bone disorders	Back pain	2 (18.2)
Nervous system disorders	Headache NOS	2 (18.2)
Reproductive system and breast disorders	Dysmenorrhea	2 (18.2)
Skin & subcutaneous tissue disorders	Pressure sore	2 (18.2)

Source: Table T42.
Note: For patients reporting the same adverse event on more than one occasion, the event was only counted once. Percentage (%) is based on total number of patients in safety population.
NOS=not otherwise specified.

Source: Table 15, *5.3.4.2.3, p 71*

Anticholinergic adverse events were reported by 3 (33%) of the subjects, with constipation, abdominal pain and vomiting each occurring in one patient. There were no reports of dry mouth.

12.8.4 Laboratory Values

The serum chemistry, hematology, and urinalysis test results were reviewed. Shifts from baseline in laboratory parameters are displayed in Table 50. No clinically significant changes in the laboratory values were noted. The elevations in potassium and ALT were minor and occurred only during dose period 3.

Table 50 Shifts from Baseline in Laboratory Safety Variables

Laboratory Variable	WEEK 4 (DAY 28)			WEEK 8 (DAY 56)			WEEK 12 (DAY 84)		
	Up	Down	Missing	Up	Down	Missing	Up	Down	Missing
Alanine Aminotransferase (ALT/SGPT)	.	1	.	.	1	.	.	.	.
Aspartate Aminotransferase (AST/SGOT)	.	.	1	.	.	1	1	.	1
Erythrocytes (Red Blood Cells, RBC)	1	1	.	2	2	.	.	1	.
Hemoglobin, mass concentration	.	1	.	.	.	.	.	.	.
Leukocytes (White Blood Cells, WBC)	.	3	.	.	.	.	.	.	.
Potassium (K)	.	.	.	.	.	.	1	.	.

Source: Table T68, *5.3.4.2.3, p 231*

Medical Reviewer's comments:

1) **Table 44 does not include values that were outside the normal range at baseline and continued in the same direction at dosing.**

2) **Two apparent errors were evident on review of the individual subjects' laboratory data. Subject 303 was reported to have an ALT value of 3 at week 8, reported as a low value. However, review of the subject's ALT trend (15 at baseline, 21 at week 4, 27 at week 12) suggests that this value was inaccurately recorded. Subject 311 is reported to have an ALT of 0.10 at week 4. This subject's preceding and succeeding values were 25 at baseline, 32 at week 8 and 27 at week 12, suggesting an error in recording.**

12.8.5 ECGs

One subject had an ECG read as abnormal but not clinically significant at baseline, with sinus tachycardia. Another subject had baseline sinus tachycardia that was not judged to be abnormal or clinically significant.

At the treatment visits, sinus bradycardia was seen in only one subject, at dose period 2, and sinus tachycardia was seen predominantly at dose period 3 (Table 51).

Table 51 ECG Rhythms by Dose Period

	Baseline N=11	Period 1, 2 mg/day N=11	Period 2, 4 mg/day N=11	Period 3, 6 mg/day N=10
Normal Sinus Rhythm	9	7	4	9
Sinus Bradycardia	0	1	0	0
Sinus Tachycardia	2	3	6	1
Not reported	0	0	1	1

Source: Table T59, *5.3.4.2.3, p 215*

Abnormal QT findings had been defined a priori as a QT interval exceeding 500 msec on any ECG or a change from baseline QT interval of greater than 60 msec. Mean and median uncorrected and corrected (Bazett) QT intervals showed no significant change over dose periods. With the Fridericia correction, QT interval in periods 2 and 3 decreased significantly from baseline (by 8-9 msec, 95% confidence limits did not include 0) (Table 52).

Table 52 Corrected and Uncorrected QT Intervals by Dose Period

		QT (msec)	QTc Fridericia (msec)	QTc Bazett (msec)
Baseline	Mean (SD)	351.5 (24.8)	385.5 (13.7)	404.3 (20.1)
	Median (min-max)	346.8 (320.8 to 397.3)	382.8 (364.0 to 409.5)	412.0 (373.5 to 444.0)
	Not reported	0	0	0
Period 1: 2 mg/day	Mean (SD)	340.7 (34.6)	378.1 (23.9)	399.0 (25.2)
	Median (min-max)	345.5 (265.5 to 401.8)	387.3 (339.8 to 409.3)	405.5 (358.3 to 441.8)
	Not reported	0	0	0
Period 2: 4 mg/day	Mean (SD)	336.5 (21.0)	377.2 (13.6)	399.8 (14.9)
	Median (min-max)	336.0 (310.7 to 367.5)	374.4 (359.8 to 403.4)	397.9 (376.8 to 422.4)
	Not reported	1	1	1
Period 3: 6 mg/day	Mean (SD)	339.1 (19.1)	376.1 (12.9)	396.6 (17.9)
	Median (min-max)	340.0 (311.0 to 375.8)	373.1 (359.5 to 397.3)	391.3 (372.3 to 425.0)
	Not reported	1	1	1
Change from Baseline to period 1	Mean (SD)	-10.8 (27.6)	-7.4 (18.1)	-5.3 (20.2)
	Median (min-max)	-13.0 (-55.3 to 34.0)	-7.0 (-39.3 to 21.0)	-3.5 (-31.3 to 29.8)
	H-L (95% c.i.)*	-10.6 (-33.9, 10.0)	-7.2 (-21.3, 5.9)	-5.8 (-20.1, 9.5)
	Not reported	0	0	0

		QT (msec)	QTc Fridericia (msec)	QTc Bazett (msec)
Change from Baseline to period 2	Mean (SD)	-12.1 (14.6)	-8.6 (7.7)	-6.6 (16.7)
	Median (min-max)	-13.3 (-32.3 to 7.3)	-8.3 (-26.0 to 2.4)	-1.4 (-42.3 to 13.1)
	H-L (95% c.i.)*	-11.9 (-24.4, 0.5)	-8.0 (-15.0, -3.2)	-4.4 (-20.9, 6.3)
	Not reported	1	1	1
Change from Baseline to period 3	Mean (SD)	-9.5 (19.6)	-9.6 (10.9)	-9.8 (15.0)
	Median (min-max)	-10.1 (-46.3 to 22.8)	-9.4 (-34.3 to 9.0)	-4.6 (-31.3 to 13.0)
	H-L (95% c.i.)*	-8.5 (-23.4, 4.4)	-8.9 (-20.1, -1.4)	-9.8 (-22.8, 1.6)
	Not reported	1	1	1

Source: Table T54a, *5.3.4.2.3, pp 204-205*

There was only one QT interval greater than 450 msec at baseline and dose period 2, and two in period 1 and period 3 and these were noted only with the Bazett correction. The two prolonged QTcB readings in period 3 occurred on two ECGs in the same subject; otherwise no prolonged QT intervals were recurrent.

QT prolongation greater than 30 msec beyond baseline was seen in 1.3 to 9.1% of ECGs, depending on the dose period and the correction used (Table 53). Changes greater than 30 msec in uncorrected QT occurred on three ECGs in a single subject at dose period 1, and in a different subject in dose period 2. The greatest change was 42.3 msec, at dose period 1. Using QTcF, only one subject had an elevation >= 30 msec in two ECGs at dose period 3, with a maximum of 39.8 msec. The QTcB correction resulted in higher frequencies of change >= 30 msec, with four ECGs in three patients showing increases during dose period 1, two subjects during dose period 2 and 2 ECGs in a single subject during dose period 3, with a maximum increase of 51 msec.

Table 53 Change from Baseline QT Interval by Dose Period

		Period 1 N=11		Period 2 N=11		Period 3 N=10	
		n	%	n	%	n	%
QT	< 30 msec	41	93.2	77	98.7	40	100.0
	>= 30 to <60 msec	3	6.8	1	1.3	.	.
QTcF	< 30 msec	44	100.0	78	100.0	38	95.0
	>= 30 to <60 msec	.	.	.	.	2	5.0
QTcB	< 30 msec	40	90.9	76	97.4	38	95.0
	>= 30 to <60 msec	4	9.1	2	2.6	2	5.0

Note: Ns refer to ECGs, not to subjects.

Source: T65, *5.3.4.2.3, p 227*

Medical Reviewer's comments:

1) **The criteria for defining a QT interval or interval change as abnormal in this study (>500 msec, >60 msec) are commonly used as thresholds for discontinuation from a trial. The results are reported by the more stringent criteria of interval >= 450 msec and change >= 30 msec. This is appropriate as the upper limit of normal QT interval in children is reported to be 450 msec in males and 460 msec in females[3]. The single QTcB interval greater than 450 was 463 and occurred during dose period 3.**
2) **The highest proportion of QT interval change from baseline > 30 msec occurred with the Bazett correction, which is known to overcorrect at higher heart rates (i.e., as seen in children).**
3) **The effect of tolterodine on the QT interval is difficult to analyze without a placebo and positive control.**

12.8.6 Vital Signs

Blood pressure, pulse, temperature and respiratory rate were obtained at each visit; however, neither composite nor individual data are reported.

Medical Reviewer's comment:

No data on vital signs evaluations are presented.

12.8.7 Gastrointestinal Function

Gastrointestinal function was assessed at each visit by patient diary reports of number of bowel movements over three days along with assessment of their consistency. Parents were also asked to comment on the subject's bowel regimen and any changes noted over the four week treatment interval. Table 54 presents the mean number of daily bowel movements and mean consistency over each treatment period. There was minimal change in the number of stools per day at each dose level. Consistency also showed minimal change at each dose period and remained in the soft, formed stool range.

Table 54 Gastrointestinal Function by Dose Period

		Mean number of bowel movements per 24 hours	Mean consistency per bowel movement
Baseline	Mean (SD)	1.3 (1.2)	2.2 (0.4)
	Median (min-max)	1.0 (0.3 to 4.3)	2.0 (2.0 to 3.0)
	Not reported	0	0
Period 1: 2 mg/day	Mean (SD)	1.6 (1.2)	2.2 (0.4)
	Median (min-max)	1.2 (0.0 to 4.3)	2.0 (1.6 to 3.0)
	Not reported	1	2
Period 2: 4 mg/day	Mean (SD)	1.6 (1.3)	2.1 (0.4)
	Median (min-max)	1.3 (0.7 to 5.0)	2.0 (1.6 to 3.0)
	Not reported	2	2
Period 3: 6 mg/day	Mean (SD)	1.5 (1.3)	2.2 (0.4)
	Median (min-max)	1.0 (0.3 to 4.7)	2.0 (2.0 to 3.0)
	Not reported	2	2
Change from baseline to period 1	Mean (SD)	0.2 (0.8)	0.0 (0.4)
	Median (min-max)	0.0 (-1.0 to 1.7)	0.0 (-0.7 to 0.7)
	H-L (95% c.i.)*	0.2 (-0.5, 0.7)	0.0 (-0.4, 0.3)
	Not reported	1	2
Change from baseline to period 2	Mean (SD)	0.1 (0.7)	-0.2 (0.4)
	Median (min-max)	0.0 (-1.0 to 1.3)	0.0 (-1.0 to 0.4)
	H-L (95% c.i.)*	0.0 (-0.5, 0.7)	-0.1 (-0.5, 0.2)
	Not reported	2	2
Change from baseline to period 3	Mean (SD)	0.1 (0.7)	-0.0 (0.5)
	Median (min-max)	0.0 (-1.0 to 1.3)	0.0 (-1.0 to 1.0)
	H-L (95% c.i.)*	0.2 (-0.5, 0.7)	0.0 (-0.5, 0.5)
	Not reported	2	2

Source: Table T50.
*95% C.I.=95% non-parametric confidence interval for Hodges-Lehman estimate.
Note: Consistency: 1=liquid, 2=soft formed stool, 3=firm hard stool. "Not reported" includes missing visits and visits with no recordings of this variable.
H-L=Hodges-Lehman estimate: Max=maximum; min=minimum; SD=standard deviation.

Source: Table 18, *5.3.4.2.3, p 79*

12.9 Reviewer's assessment of efficacy and safety

In Study 003, administration of tolterodine prolonged release capsules for 12 weeks for the treatment of detrusor hyperreflexia was demonstrated to be safe in 11 pediatric patients with neurogenic lower urinary tract dysfunction, aged 11 to 15 years of age. No new and unlabeled safety issues were identified.

Determination of efficacy in this population is compromised by the methodological limitations of the study. First, the study is uncontrolled (i.e., there is no placebo group) and non-randomized. The sample size is small and there is a large amount of missing data, particularly on the urodynamic assessments, which makes interpretation difficult. Even accepting these limitations, the efficacy data do not provide clear evidence of a benefit to use of tolterodine.

Reviewing the urodynamic data, apparent dose-response trends are noted in one of 9 variables assessed – intravesical volume at 30 cm H_20. However, the increase over baseline is not statistically significant at any dose level. The only statistically significant finding is the increase in functional bladder capacity at dose levels 1 and 3 (although the increase at dose level 1 is greater than that at dose period 3). Looking at the individual urodynamic data for functional bladder capacity, which would perhaps be the most easily interpretable parameter that would be expected to improve under treatment, 9 of 11 subjects showed improved values on treatment as compared to baseline (one had data only at dose level 1), but only 2 of 10 demonstrated a dose-response relationship (and even they did not follow the dose-response trend at one dose period).

Similarly, the patient diary data showed a statistically significant dose-related reduction at all dose levels only in the number of daily incontinence episodes, although the overall dose-response trend was not statistically significant. The mean number of daily catheterizations or micturitions was essentially unchanged. None of the measures showed a clear dose-response trend. Reviewing individual data, 9 of the 11 patients had decreased number of incontinence episodes over baseline while on treatment. Only 4 of the 11 showed a dose-response trend, although two of them failed to follow the trend at the highest dose level.

No clear relationship between drug exposure and urodynamic or patient diary results was identified. This apparent lack of an association between exposure and efficacy in pediatric patients with neurogenic lower urinary tract dysfunction for the treatment of detrusor hyperreflexia makes it difficult to determine an optimal dosing regimen.

Appendix B: TRIALS IN URINARY URGE INCONTINENCE

13 CLINICAL TRIAL 583E-URO-0084-020

13.1 Summary

Title: "Clinical Efficacy and Safety to Tolterodine Prolonged Release Capsules 2 mg qd. Compared to Placebo in Children with Symptoms of Urinary Urge Incontinence Suggestive of Detrusor Instability" dated January 16, 2002.

Three amendments were made to Study 020. The first, dated May 31, 2000, included the following changes:

- Included hematology and clinical chemistry labs at Visits 2 and 4
- Added genotyping for metabolizer status at Visit 2
- Added ECGs on all subjects at Visit 2 and on all poor metabolizers and 10% of extensive metabolizers at Visit 4
- Added serum levels of tolterodine and DD01 at Visit 4
- Added post-treatment follow-up contact one week after completion of the study for subjects not continuing in the extension study

Amendment #2, dated August 24, 2000, included the following changes:

- Added ECGs on all subjects at both Visits 2 and 4
- Lowered the age limit for inclusion from 6 years to 5
- Added a dipstick urinalysis to Visits 1, 2 and 4
- Added ectopic ureteral insertion or continuous dribbling to the exclusion criteria

Amendment #3, dated March 1, 2001, included the following changes:

- Added the variable "dampness episodes" to the incontinence outcome variables
- Clarified the difference between variables "incontinence episodes" and "dampness episodes"
- Allowed subjects unable to swallow the capsule to open it and swallow the beads with food
- Changed the blood volume drawn for genotyping at Visit 2

Medical Reviewer's comment:

1) **The addition of a variable "dampness episodes" was not adopted in the UK. Therefore, subjects at these sites were coded as having an "incontinence episode" whether they were damp or fully incontinent.**

First patient entered: December 8, 2000

Last patient completed: July 6, 2001

13.2 Objectives

The primary objective of this study was:

- to compare the clinical efficacy of tolterodine PR 2 mg daily with placebo in reducing the number of weekly incontinence episodes in children with symptoms of urinary urge incontinence suggestive of detrusor instability.

The secondary objectives were:

- to compare the clinical efficacy of tolterodine PR with placebo in reducing number of micturitions/day, and in increasing urinary volume/void, well-being as measured by a visual analog scale and parent-assessment of treatment benefit.
- to compare safety of tolterodine PR with placebo, evaluating adverse events and study withdrawals, post-void residual urine volume (PVR), clinical laboratory and ECG findings and serum concentrations of tolterodine and its active metabolite.

13.3 Overall Design

This Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled 12-week treatment duration, study was designed to evaluate the clinical efficacy and safety of tolterodine PR daily in 342 pediatric subjects aged 5 to 10 years, inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability. Subjects were randomized to tolterodine or placebo in a 2:1 ratio. Eligible subjects went through a one-week wash out from their current medication and a one-week run-in period. Efficacy data were collected based upon a micturition chart completed twice over a seven-day period. Upon completion of the study, subjects were eligible to enter a 12-month open label safety extension study, or were followed for 1 week post-treatment.

The study was conducted at 44 sites in Europe and Asia (Austria, Belgium, Denmark, Germany, Hong Kong, Norway, Russia, Slovenia, Sweden, The Netherlands and the U.K.). The recruitment goal was 300 subjects, 200 to receive tolterodine, 100 to receive placebo, with approximately equal numbers in the 5-7 and 8-10 year old groups.

13.4 Study Procedures and Conduct

13.4.1 Schedule of Study Assessments

During the Wash-out/Run-in Visit (Visit 1), informed consent and assent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after performing a history, physical examination, vital signs, and urinalysis. A micturition diary was given to subjects and they were given two placebo capsules to assess their ability to swallow them. Subjects were randomized and study medication dispensed at Visit 2 after an ECG and labs and urinalysis were taken and baseline PVR and micturition chart was assessed. All patients returned to the clinic for study assessments according to the schedule presented in Table 55.

Table 55 Schedule of Study Assessments

Part of study	Wash-out / run-in	Inclusion	Treatment period			Post-treatment
Visit	1	2	Telephone contact	3	4	Telephone contact/ Visit 5 *
Time in study (days)	– 14 and – 7 °	0	7 – 14	24 – 32	80 – 88	+ 7
Written informed consent	X					
Demography and vital signs	X					
Medical history/ physical findings	X					
Urological history	X					
Concomitant medication	X	X	X	X	X	X
Adverse events			X	X	X	X
Blood sample (clinical chemistry, hematology, and CYP2D6 genotyping §)		X			X	
Blood sample (tolterodine and DD 01 metabolite)					X	
Urine dipstick test	X	X			X	
MSU for culture and microscopy	X	X ¶			X	
PVR urine volume		X		X	X	
ECG		X			X	
Dispensing of 2 placebo capsules	X					
Inclusion / exclusion criteria		X				
Randomization		X				
Drug dispensing		X		X		
Compliance to treatment				X	X	
Drug accountability				X	X	
Dispensing of micturition chart	X			X		
Collection of micturition chart		X			X	
VASC		X			X	
Benefit of treatment					X	

* Subjects who did not continue into the open-label extension study (583E-URO-0084-021) had a follow-up visit or telephone contact.

° Subjects who did not receive any treatment for detrusor instability in the 7 days prior to Visit 1 could omit the 7-day wash-out period and directly enter the 7-day run-in period.

‡ In addition to AE reporting at the post-treatment follow-up, drug-related or serious adverse events were followed until they resolved or were judged to be "stable" or "chronic".

§ CYP2D6 genotyping was performed at Visit 2 only.

¶ Performed if the urine dipstick test was positive for leukocytes at Visit 2.

Source: Table 8-1, *5.3.5.1.1, p38*

13.5 Study Drug

13.5.1 Dose Selection

The drug studied was tolterodine prolonged release (PR) 2 mg capsules, taken once daily. This dose was chosen after comparison of the pharmacokinetics of tolterodine and DD 01 in children aged 5-10 and adults showed that a daily total of 2 mg of tolterodine immediate release (IR) in children produced exposure equivalent to that seen in adults taking a daily total of 4 mg of tolterodine IR (both dosed BID). One-half of the adult dose of tolterodine PR was therefore used in this study.

The drug was to be taken daily in the morning and preferably swallowed whole with water. If a child was unable to swallow the capsule, it was allowed to be opened and the beads taken with food.

Medical Reviewer's comment:

There is no description in the study report of the number of children unable to swallow capsules who therefore took the drug or placebo in bead form. Study 004 showed that these two methods of ingestion may not produce bioequivalence, as measured by Cmax. There is also no analysis evaluating differences in outcome according to method of ingestion.

13.5.2 Choice of Comparator

The study was placebo-controlled. Placebo was delivered in a capsule identical to the study drug.

13.5.3 Assignment to Study Drug

Subjects were randomized to tolterodine or placebo in a 2:1 ratio at Visit 2 by a random permuted block method with block size of 3. Study medication was prepackaged according to the randomization list and a multiple of the block size was delivered to each center. Double-blinding was maintained until closure of the database.

13.6 Patient Population

13.6.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or female, aged 5 to 10 years, inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability, defined by one or more episodes of incontinence or dampness daily during waking hours for at least 5 of 7 days, as confirmed by the run-in micturition chart

2. Body weight and height within the normal range (between 5-95th percentile for weight and above 5th percentile for height) according to national standardized growth curves of the participating countries

3. Participants/parents(s)/legal guardians(s) able to understand and cooperate with information given and who have provided written consent to participate in the study

4. Subjects who are able to swallow the capsules and able to complete the micturition chart

Medical Reviewer's comment:

The requirement that subjects be able to swallow the capsule was later amended, as noted above, to allow subjects to open the capsule and consume the beads.

Exclusion Criteria

1. Any condition which, in the investigator's opinion, made the subject unsuitable for inclusion

2. Nocturnal enuresis or "giggle incontinence" or overactive bladder of neurogenic origin

3. Fewer than 2 micturitions/day during the run-in charting period

4. UTI at visit 1, a history of urinary retention, or PVR >= 20% of theoretical bladder capacity on at least 2 bladder scans at Visit 2

5. Known significant anatomic abnormalities of the urinary tract, significant anatomic or functional bladder outlet obstruction, or history of surgery to the bladder neck or urethra

6. Severe constipation not responding to oral treatment

7. Post-menarchal females

8. Recent history of significant hepatic or renal disease, uninvestigated hematuria or diabetes insipidus

9. An indwelling catheter or practicing clean intermittent catheterization

10. Participants taking any medications known to affect the lower urinary tract (except desmopressin for nocturnal enuresis) or anticholinergic drugs or on an unstable dose of any drug with anticholinergic side effects

11. Treatment with any drug for detrusor instability or with electrostimulation therapy or bladder training within 14 days of randomization

12. Any contraindications to or intolerance of anticholinergic therapy

13. Participants who have taken an investigation drug within a period of two months prior to study entry or who have previously participated in this study

14. Participants with known allergy or hypersensitivity to tolterodine or its excipients

15. Participants who are currently taking antibiotics which interact with CYP3A4 metabolism such as antifungals or aminoglycosides

13.6.2 Demographics and Baseline Disease Characteristics

Forty-four European and Asian sites each enrolled 1 to 33 subjects. Belgium accounted for almost one-fourth of the subjects. As expected by the block randomization, subjects were distributed in a 2:1 ratio between tolterodine and placebo within each country. Table 56 provides the breakdown by country for the 342 subjects in the Intention to Treat population (ITT). The Per Protocol population (PP) excludes the 23 and 17 subjects who withdrew from the tolterodine and placebo groups, respectively.

Table 56 Subject Enrollment by Country

Country (no. of centers)	Treatment Group		
	Placebo (n)	Tolterodine PR 2 mg q.d. (n)	Total (n)
Austria (4)	7	15	22
Belgium (8)	28	55	83
Denmark (3)	9	19	28
Germany (3)	4	10	14
Hong Kong (1)	5	8	13
Netherlands (5)	7	18	25
Norway (4)	13	30	43
Russian Federation (3)	9	25	34
Slovenia (1)	4	8	12
Sweden (2)	6	11	17
United Kingdom (10)	15	36	51
Total (44)	107	235	342

Source: Table 9-1, *5.3.5.1.1, p 53*

Baseline demographic and baseline characteristics for the ITT population are summarized in Table 57 and Table 58. The trial enrolled a slight plurality of males. Over 90% were Caucasian, with almost all the remaining subjects being Asian/Pacific Islander. In the 5-7 year old group, there were 55 placebo and 123 tolterodine-assigned subjects; in the 8-10 year old group, these numbers were 52 and 112. Eighty-five or more percent were extensive metabolizers. Median treatment group weight was 25.0 kg (range 15.9-44.0 kg), while median placebo group weight was 27.0 kg (range 15-62.6 kg). Almost half of each group had received previous medical treatment for urinary urge incontinence and less than half of each had experienced good efficacy of this treatment. Treatment and placebo subjects were similar on baseline number of weekly incontinence episodes, percent reporting gross incontinence, greater than 7 micturitions/24 hours and number of dry days/week.

Medical Reviewer's comments:

1) **The placebo group was heavier, with a higher BMI.**

2) **The tolterodine group had a higher proportion of those subjects who had experienced good efficacy on previous medication therapy for urinary urge incontinence. This could result in unequal assignment of likely responders to the treatment group rather than the placebo group.**

Table 57 Demographic Characteristics of ITT Population

Demographic Characteristic		Treatment Group	
		Placebo (n=107)	Tolterodine PR 2 mg q.d. (n=235)
Sex, n (%)	Male	59 (55.1)	127 (54.0)
	Female	48 (44.9)	108 (46.0)
Age (years)	Mean (SD)	7.9 (1.6)	7.9 (1.5)
	Median (min-max)	7.9 (4.6 to 11.0)	7.9 (5.0 to 10.9)
	Subjects not reporting	0	1
Age group (years), n (%)	4 – 6	34 (31.8)	72 (30.6)
	7 – 8	41 (38.3)	99 (42.1)
	9 – 11	32 (29.9)	64 (27.2)
Race, n (%)	White	100 (93.5)	218 (92.8)
	Asian or Pacific Islander	7 (6.5)	13 (5.5)
	Mixed/Multiracial	0	4 (1.7)

Source: Table 9-5, *5.3.5.1.1, p 60*

Table 58 Baseline Characteristics of ITT Population

Baseline Characteristic		Treatment Group	
		Placebo (n=107)	Tolterodine PR 2 mg q.d. (n=235)
Weight (kg)	Mean (SD)	26.1 (6.2)	28.0 (7.4)
	Median (min-max)	25.0 (15.9 to 44.0)	27.0 (15.0 to 62.6)
	Subjects not reporting	0	0
Weight group	<20 kg, n (%)	18 (16.8)	28 (11.9)
	≥20 kg and <30 kg	62 (57.9)	129 (54.9)
	≥30 kg, n (%)	27 (25.2)	78 (33.2)
Height (cm)	Mean (SD)	126.6 (11.6)	128.5 (10.3)
	Median (min-max)	126.2 (102.5 to 152.4)	128.6 (102.5 to 157.0)
	Subjects not reporting	0	0
BMI (kg/m^2; calculated)	Mean (SD)	16.1 (1.7)	16.7 (2.4)
	Median (min-max)	15.7 (13.0 to 21.5)	16.4 (10.6 to 27.3)
	Subjects not reporting	0	0
Metabolizer phenotype	Extensive, n (%)	91 (85.0)	208 (88.5)
	Poor, n (%)	7 (6.5)	11 (4.7)
	Subjects not reporting, n (%)	9 (8.4)	16 (6.8)
Previous medical treatment for OAB?	No, n (%)	55 (51.4)	126 (53.6)
	Yes, n (%)	51 (47.7)	108 (46.0)
	Subjects not reporting, n (%)	1 (0.9)	1 (0.4)
Efficacy of previous OAB treatment *	Poor, n (%)	35 (68.6)	60 (55.6)
	Good, n (%)	15 (29.4)	47 (43.5)
	Subjects not reporting, n (%)	1 (2.0)	1 (0.9)

* Among subjects who had previous OAB treatment.

BMI = body mass index; ITT= intent to treat; min = minimum; max = maximum; OAB = overactive bladder; PR = prolonged release; q.d. = once daily; SD = standard deviation.

Source: Table 9-6, *5.3.5.1.1, pp 60-61*

13.6.3 Withdrawals, compliance, and protocol violations

Twenty-three tolterodine and 17 placebo subjects discontinued the trial early (Table 59). The difference in withdrawal rate was not significant between the two groups (p=0.10). Five and 11 subjects, respectively, in the placebo and tolterodine groups withdrew due to adverse events (see Section 13.8.3). The primary reason for withdrawal in the placebo group was consent withdrawal (47%); in the tolterodine group, it was adverse events (48%).

Table 59 Reasons for Withdrawal by Group

Reason for Withdrawal	Treatment Group			
	Placebo (n = 107)		Tolterodine PR 2 mg q.d. (n = 235)	
	n	%	n	%
Adverse event	5	4.7	11	4.7
Protocol violation	1	0.9	4	1.7
Consent withdrawn	8	7.5	5	2.1
Lost to follow-up	3	2.8	3	1.3
Total	17	15.9	23	9.8

Source: Table 9-2, *5.3.5.1.1, p56*

Compliance was assessed by comparison of expected number of capsules taken to amount of unused study medication returned at Visits 3 and 4. Compliance was defined as actual use >=75% of expected use. Two placebo subjects and six tolterodine subjects were determined to be <75% compliant, giving compliance rates of 85% in the placebo group and 90% in the treatment group.

Medical Reviewer's comments:

1) **It is later stated (p 65 of the study report, *5.3.5.1.1*) that compliance "is based on the drug accountability data and time in study." It is unclear how time in study affected compliance determination.**

2) **Drug dispensing occurred at Visit 2 and Visit 4 (24-32 days into the study). It appears that 40 capsules were dispensed at Visit 2 and 120 at Visit 4. The compliance rates in those subjects who did not complete the study are affected by the time of withdrawal. For example, compliance rates as high as 234-387% are attributed to subjects who withdrew shortly after visit 4 and likely failed to return any capsules. It is highly unlikely that their actual compliance approached these levels.**

3) **In reviewing the individual compliance data, only 5 subjects in the tolterodine group are identifiable by a compliance rate <75%.**

Protocol violation criteria were defined a priori and subjects categorized as violators prior to unblinding. Major protocol violations occurred in 29 placebo subjects (27%) and in 60 treatment subjects (26%). Specific violations are noted in Table 60. The vast majority concern unusable micturition chart data.

Table 60 Major Protocol Violations by Group

Protocol Violation*	Treatment Group			
	Placebo (n = 107)		Tolterodine PR 2 mg q.d. (n = 235)	
	n	%	n	%
Subject does not have at least 1 incontinence episode for at least 5 of 7 days during run-in†	6	5.6	7	3.0
Subject has ≤ 2 micturitions/day during run-in †	0		2	0.9
Exclusion criteria 11 and 17	0		1	0.4
Missing, incomplete, or invalid micturition chart	25	23.4	47	20.0
On treatment <70 or >120 days‡	0	0	2	0.9
Compliance < 75%	2	1.9	6	2.6
Use of prohibited concomitant medication	0		5	2.1
Total no. (%) of subjects with major violation(s)	**29**	**27.1**	**60**	**25.5**

* Subjects may have more than one major violation.

†For two subjects both baseline and end of treatment micturition charts were judged invalid, and for one subject the baseline micturition chart was invalid, these three subjects are not included

‡Withdrawals not included

Source: Table 9-3, *5.3.5.1.1, p 57*

Medical reviewer comments:

The absence or unreliability of 20% of the data used for several of the major efficacy endpoints is a significant review issue. If micturition chart data were missing, the last observation carried forward (LOCF) technique was used to impute missing values. In this case, since the "last observation" occurred at baseline, the LOCF technique would tend to minimize treatment differences if applied to a significant proportion of the data.

13.7 Efficacy

13.7.1 Key Efficacy Assessments

The clinical efficacy variables were based on the micturition charts, and on the Visual Analog Scale for Children for subjects 9 years or older. The VASC is reported to be a validated questionnaire with six subscales used to measure the subject's well-being (alertness, self-esteem, mood, inhibition, stability and litheness). This scale was administered only to those subjects aged 9 and greater.

Parental assessment as to the benefit from treatment was also assessed, rated as "no," "little" or "much" improvement. The micturition charts were completed for 7 days at run-in, and over the final 7 days preceding Visit 4. Variables from the charts were:

- Number of "gross" incontinence episodes during waking hours
- Number of "dampness episodes" during waking hours (this variable was not used for U.K. subjects)
- Number of micturitions
- Urinary volume voided (using a measuring vessel provided to the subject)
- Whether the prior night was "wet" or "dry"

Data obtained during a period when the investigator suspected a UTI were excluded if the UTI were confirmed by culture or if no culture were available.

Additional, exploratory, analyses pre-specified in the protocol included subgroup analysis for age and gender, and exploration of possible relationships between BMI and efficacy/safety variables and between baseline urinary frequency and age, sex and micturition chart variables.

Medical reviewer comments:

1) **Although generally the micturition chart data were collected over 7 days, the volume/void was measured on only 2 of the 7 diary days. It is not specified which two days were chosen, whether they were consecutive and whether the choice of days was made by the subject/parent, by the investigator, or pre-specified in the protocol.**
2) **Data collected during a culture positive UTI occurring when the investigator had not suspected a UTI were included. This introduces a possible bias, as variables in the micturition chart may influence the investigator's suspicion of UTI.**
3) **Review of the literature cited in support of the VASC, it appears that the psychometric properties of this instrument were assessed using a population of children with short stature, not incontinence.**

13.7.2 Pharmacokinetic Assessments

Serum samples for pharmacokinetics were to be obtained at Visit 4 (or at withdrawal), within 3-9 hours following the last dose of study medication. PK data from Study 020 was not analyzed separately, but was pooled with data from Study 008; the pooled analysis is discussed in Section 5.1.2.4.

13.7.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was change from baseline to week 12 in number of weekly incontinence episodes during waking hours (both "gross" and "dampness" episodes). The analysis was conducted on the ITT population, with exclusion of two patients' (one who received placebo and one who received tolterodine) micturition diary data, which were found to be "invalid" at baseline and end of treatment.

Data on reduction in the number of weekly incontinence episodes are shown in Table 61. A significant decrease in episodes occurred in both groups, and the difference in the treatment group was not statistically significantly greater than that in the placebo group (p=0.07). The analysis was repeated excluding the 53 subjects in the UK sites, for whom the amendment describing "dampness episodes" did not apply. The placebo results were unchanged, there was a slightly larger decrease in all incontinence episodes in the treatment group, and the difference between groups approached significance (p=0.052). Per protocol analyses were also performed, both with and without the UK data, and significance was not reached in either.

Medical Reviewer's comments:

1) **The nature of the "invalid" micturition chart data for two subjects, who were excluded from analysis of efficacy variables based on the chart, is not described, nor are the subjects identifiable in the report.**

2) **The validity of excluding data from the UK is questionable. The study report notes that the "dampness" variable was added after review of baseline diaries suggested that some subjects were classifying gross incontinence episodes as "dampness." The change was not made in the UK due to Ethics Board considerations. However, on p 39 of the study report, *5.3.5.1.1*, it is specified that "In the UK, all episodes of wetting were to be recorded as incontinence." It would therefore seem that the UK data for incontinence episodes would be comparable to the data from the other sites for "gross + dampness" episodes (and in fact, this is acknowledged on p 72 of the study report), and thus, there would be no rationale for excluding UK data.**

Table 61 Change in Weekly Incontinence Episodes

Number of Incontinence Episodes/Week	Treatment Group	
	Placebo (n = 107)	Tolterodine PR 2 mg q.d. (n = 235)
Missing	1	1
Baseline		
Mean (SD)	13.8 (8.0)	14.2 (9.3)
Median (min – max)	12.0	11.4
Week 12		
Mean (SD)	10.0 (8.7)	8.9 (9.1)
Median (min – max)	8.0	7.0
Change from baseline to Week 12		
Mean (SD)	-3.8 (6.1)	-5.3 (7.6)
Median (min – max)	-3.0	-4.7
p-value	<0.0001	<0.0001
Treatment difference		
Estimated difference in mean change (SEM)	-1.54 (0.84)	
95% confidence interval	-3.19, 0.12	
p-value	0.0689	

ITT = intent to treat; LOCF = last observation carried forward; max = maximum; min = minimum; PR = prolonged release; q.d. = once daily; SD = standard deviation; SEM = standard error of the mean.

Source: Table 9-13, *5.3.5.1.1, p 68*

Exploratory analysis evaluating the effect of baseline urinary frequency was also undertaken. Subjects were divided by baseline frequency of seven or fewer micturitions/24 hours, or greater than 7 episodes/24 hours. The "normal frequency" subgroup comprised 229 subjects (75 placebo, 154 tolterodine), or about 67% of the total population. These subjects showed no benefit from tolterodine treatment as compared to placebo. The "pathological frequency" group, which included a slightly smaller proportion of placebo subjects (30% of placebo group fell into this category vs. 34% of the tolterodine group), did show a significant difference between tolterodine and placebo in the reduction in number of incontinence episodes at week 12. The tolterodine subjects averaged 6.7 fewer incontinence episodes weekly as compared to baseline frequency; while the placebo subjects averaged only a 2.5 weekly episode reduction (p=0.04).

Multiple regression models were also generated to evaluate predictors of change from baseline in frequency of weekly incontinence episodes. Including independent variables for treatment group, baseline number of incontinence episodes, baseline mean number of micturitions in 24 hours, baseline

mean volume/void, sex, age, weight and BMI, the model found that only the baseline weekly frequency of incontinence was a significant predictor of outcome; treatment group had a p value of 0.09. Additional subgroup analyses suggested a benefit to tolterodine treatment in a subgroup of subjects defined by having 10 or more weekly incontinence episodes at baseline and at least 6 micturitions/day.

Finally, subgroup analyses were also performed to look at the effect of age, sex and body weight on number of weekly incontinence episodes. There were significant differences favoring efficacy of tolterodine in children aged 4-6 years and in males, although in both groups, the change from baseline in the placebo group was smaller than that seen in older children and in males, respectively. Sub-analysis by body weight did not reveal any effect of body weight as categorized as <20 kg, 20 to 30 kg and >30 kg. Table 62 presents the results of ITT and subgroup analyses on the primary and secondary efficacy assessments.

Table 62 Change from Baseline and Significance in Efficacy Endpoints by Treatment Group

Endpoint	Population	Change in Tolterodine Group	Change in Placebo Group	p Value
# Weekly Incontinence Episodes	ITT	-5.3	-3.8	0.07
	>7 mict/d	-6.7	-2.5	**0.04**
	<=7 mict/d	-4.7	-4.3	0.65
	4-6 y/o	-5.5	-2.3	**0.03**
	7-8 y/o	-5.2	-4.7	0.74
	9-11 y/o	-5.3	-4.3	0.40
	Males	-5.1	-2.9	**0.02**
	Females	-5.5	-5.0	0.69
# Micturitions per 24 Hours	>7 mict/d	-1.8	-1.5	0.63
	<=7 mict/d	-0.2	0	0.45
Urine volume Per Void	>7 mict/d	19.0	1.4	**0.02**
	<=7 mict/d	11.0	7.6	0.47
# Gross Wkly Incontinence Episodes	ITT	-3.6	-2.7	0.33
# Dry Nights	ITT	0.4	0.5	0.77
# Dry Days	ITT	1.9	1.6	0.16
Any Treatment Benefit	ITT	61.8%	46.5%	**0.01**

Bold = significant result
Source: Tables 9-13 to 9-19 , 13-17 , *5.3.5.1.1, pp 68-78, 120*

13.7.4 Secondary Efficacy Endpoint Analysis

Secondary endpoints were mean change from baseline to week 12 in number of "gross" incontinence episodes, number of micturitions/24 hours, urinary volume/void, well-being as assessed by the VASC and parental assessment of treatment benefit (none, little, much). Results on the secondary endpoints generally did not demonstrate an efficacy advantage in the treatment group. Number of micturitions per 24 hours was not reported for the entire ITT group; rather, a subgroup analysis based on urinary frequency at baseline (7 or fewer micturitions/24 hours vs. greater than 7/24 hours) was conducted. Results were not significant in either sub-group; there was essentially no change in the "normal

frequency" group and decreases of similar magnitude occurred in both the treatment and placebo groups among the "pathological frequency" subgroup.

Similarly, only subgroup analyses are presented for the variable urinary volume/void. Increases were seen for both placebo and treatment groups in the "normal frequency" subgroup, and the difference between the two was not significant. In the "pathological frequency" subgroup, volume was significantly increased only for the treatment group, and a p value of 0.01 was achieved for the treatment difference. This significant difference was maintained even after controlling for higher baseline volume in the tolterodine "pathological frequency" subgroup.

Data on the number of weekly "gross incontinence" episodes are presented for the overall ITT population. The frequency of this outcome decreased significantly in both the placebo and tolterodine groups, and was not significantly different between groups (p=0.33). This analysis did exclude subjects who reported no episodes of "gross" incontinence at baseline. Results were similarly non-significant when analyzed excluding the UK data or when looking at the UK data alone.

Additional endpoints evaluated and found not to differ significantly between treatment groups included: number of dry nights, number of dry days/week, and proportion of subjects who achieved full continence at week 12.

The VASC scale was administered only to subjects aged nine or older, or approximately one-third of the ITT population. Significant differences were not found between treatment and placebo on any of the six subscales.

Parental perception of treatment benefit is presented in Table 63. The percent of parents who reported some benefit (i.e., little or much) from treatment was statistically greater in the tolterodine group than the placebo group (p<0.01).

Table 63 Parent-Perceived Treatment Benefit by Group

Perception of Treatment Benefit	Treatment Group					
	Placebo (n = 107)			Tolterodine PR 2 mg q.d. (n = 235)		
	N	%		N	%	
None	53	49.5*	53.5	87	37.0*	38.2
Any Benefit	46	43.0*	46.5	141	60.0*	61.8
Little	26	24.3*	26.3	79	33.6*	34.6
Much	20	18.7*	20.2	62	26.4*	27.2
Missing	8	7.5*		7	3.0*	
Treatment difference						
Estimated difference in percentage with any benefit, missing excluded (%)			15.4			
95% confidence interval			3.7, 27.1			
p-value, missing excluded (chi-square test)			0.0098			
p-value, missings included (chi-square test)			0.0064			
p-value (Wilcoxon rank sum test, on all categories)			0.0170			

*Missings included

Source: T 9-19, *5.3.5.1.1, p. 78*

Medical Reviewer's comments:

1) **Data on change in number of micturitions/24 hours and volume/void should be presented for the entire ITT population. Sub-group analyses are exploratory and should not be the only analyses reported.**
2) **It appears that 11 placebo and 25 tolterodine subjects were excluded from analysis of frequency of "gross" incontinence episodes because they failed to report any such episodes at baseline.**
3) **The clinical significance of "little" benefit reported by parents is uncertain. The only statistical test provided is for the contrast of No benefit to Any benefit; the significance of "Much" benefit vs. "None or little" benefit is not evaluated. In fact, among those who experienced any benefit, the proportion of those who experienced "much" benefit (as opposed to "little" benefit) is almost the same in each group: 20 of 46 or 43% in the placebo group and 62 of 141 or 44% in the treatment group.**

13.7.5 Pharmacokinetic Data Summary

A pooled PK analysis was conducted for Studies 020 and 008 and is reviewed in Section 5.2

13.8 Safety

13.8.1 Safety Measurements

All participants who received at least one dose of study medication were to be included in the summaries and listings of safety data (N=342). Adverse events were coded according to the Medical Dictionary for Regulatory Action (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events (by participant, parent, or guardian)
- Laboratory assessment (hematology, serum chemistries, and CYP2D6 genotyping): at Visits 2 and 4 (genotyping only at visit 2)
- Urinalysis, with microscopy and culture if dipstick positive, done at Visits 1, 2 and 4
- Post void residual urine volume (PVR), measured by bladder ultrasonography at visits 2, 3 and 4. A positive scan was defined as >=20% of the theoretical bladder capacity, computed by [30 + (30*age)].
- 12-lead ECG at Visits 2 and 4 (or at withdrawal), with the final ECG taken 3-9 hours after the last dose of study medication

Medical Reviewer's comment:

A different formula to calculate theoretical bladder capacity was used in Studies 001-003. No references are cited for either formula.

13.8.2 Extent of exposure

Time in study for the two groups is displayed in Table 64. At each time-point, a slightly greater percentage of the treatment group remained in the study. There was a significant decrease in sample size in the last two weeks of the study in both groups.

Table 64 Treatment Duration by Group

Duration of Treatment (days)	Treatment Group	
	Placebo (n = 107)	Tolterodine PR 2 mg q.d. (n = 235)
n	106	234
Mean (SD)	77.4 (22.8)	81.9 (17.0)
Median	84	84
25th - 75th percentiles	82 – 88	82 – 89
≥ 14, n (%)	102 (95%)	232 (99%)
≥ 28, n (%)	98 (92%)	226 (96%)
≥ 42, n (%)	92 (86%)	220 (94%)
≥ 56, n (%)	91 (85%)	217 (92%)
≥ 70, n (%)	91 (85%)	215 (92%)
≥ 84, n (%)	65 (61%)	147 (63%)
Could not be calculated	1 (0.9%)	1 (0.4%)

Source: Table 9-11, *5.3.5.1.1, p 65*

Medical Reviewer's comment:

Table 59 shows 17 placebo and 23 tolterodine subjects as having withdrawn early from the study. Since the study ran for 12 weeks (84 days), one would expect 90 placebo and 212 tolterodine subjects to remain in the study at >=84 days. The discrepancy of 90 subjects (25 placebo and 65 tolterodine) is not explained. The study visits could occur within +/- four days of the expected visit date (p 33 of study report *5.3.5.1.1)* and Visit 4 was scheduled on the day the last dose of study medication was taken; it is possible that the discrepancy in the number of subjects expected to remain in the study at 84 days is due to subjects who had their Study 4 visit on days 80-83. There do not appear to be individual listings defining the exact time at which study participation ended for subjects who were not withdrawn prematurely.

13.8.3 Serious adverse events

Deaths: there were no deaths.

Premature termination due to safety reasons: Five placebo and 11 tolterodine subjects terminated prematurely from the study because of adverse events. They are listed in Table 65. The five subjects in the placebo group suffered six adverse events, one moderate and five severe, three of which were judged to be treatment-related (2 manifestations of ocular effects in one subject and pyelonephritis). Fourteen adverse effects occurred in the eleven treatment subjects, five mild, five moderate and four severe. All but one mild event (weight gain) were judged to be treatment related. The most common adverse events leading to withdrawal were difficulty in micturition (3), urinary tract infections (2), aggressive behavior (2) and headache (2). The adverse events occurred throughout the study period, although more occurred earlier in the treatment course (five in the first month).

Table 65 Withdrawals due to Adverse Events

Sub. No. Age/Sex/ Race [*]/ Wt (kg)	Adverse Event (Preferred Term)	Onset Day/ Duration (days)	Intensity	Related to Treatment?	Outcome [†]
Placebo					
175 9/M/W/23	Fatigue	19 / 38	Severe	No	Recovered
322 9/F/W/31	Photophobia	5 / 25	Severe	Yes	Recovered
	Eye irritation	10 / 20	Moderate	Yes	Recovered
379 8/M/W/29	Femur fracture NOS [‡]	44 / 99	Severe	No	Recovered
494 10/F/W/44	Urinary incontinence aggravated	1 / Unk	Severe	No	Not recovered
654 6/F/W/21	Pyelonephritis NOS [‡]	24 / 10	Severe	Yes	Recovered
Tolterodine PR 2 mg q.d.					
285 6/M/W/24	Urinary tract infection NOS	33 / 10	Mild	Yes	Recovered
296 10/F/W/24	Urinary tract infection NOS	19 / 7	Moderate	Yes	Recovered
310	Mood alteration NOS	6 / Unk	Severe	Yes	Not recovered
11/F/W/39	Aggression	13 / 39	Severe	Yes	Recovered
316 10/M/W/28	Abnormal behavior NOS	Unk / Unk	Severe	Yes	Recovered
	Aggression	41 / 7	Severe	Yes	Recovered
321 10/M/W/39	Headache NOS	31 / 73	Moderate	Yes	Recovered
386 7/M/W/25	Weight increased	Unk / Unk	Mild	No	Recovered
392 8/F/W/23	Difficulty in micturition	77 / Unk	Mild	Yes	Unknown
487 9/F/W/38	Difficulty in micturition	26 / Unk	Moderate	Yes	Not recovered
504 9/F/W/30	Headache NOS	10 / 5	Mild	Yes	Recovered
	Abdominal pain NOS	13 / 2	Mild	Yes	Recovered
515 7/M/W/28	Difficulty in micturition	28 / Unk	Moderate	Yes	Not recovered
619 8/F/W/33	Blister	63 / 5	Moderate	Yes	Recovered

[*] Race abbreviations include: W = white.

[†] At follow-up after end of study treatment.

[‡] Serious adverse event.

Source: Table 9-30, *5.3.5.1.1, p 95*

Serious adverse events: There were four tolterodine and two placebo group subjects who experienced serious adverse events. They are listed in Table 66. None of the SAEs occurring in the tolterodine group resulted in withdrawal, and none were considered treatment related. SAEs occurred in four females, 2 males and tended to occur in younger and smaller children (ages 6-8, weights 19-29 kg).

Details of the individual cases are:

- #379 – broken femur resulting from a ski accident
- #654 – hospitalized with fever and abdominal pain, diagnosed with pyelonephritis

- #105 – decreased visual acuity in left eye diagnosed on first routine visual screening exam (seven days after starting treatment)
- #112 – hospitalized for evaluation after hit in head with stone; head CT normal
- #334 – hospitalized for fever and back pain, which resolved with IV antibiotics. Subject had past history of recurrent UTI, urine culture apparently not done
- #583 – hospitalized with fever, fatigue, stomachache, diagnosed as pyelonephritis

Table 66 Serious Adverse Events by Treatment Group

Sub. No. Age/Sex/ Race [*]/ Wt (kg)	Adverse Event (Preferred Term)	Withdrawn Due to AE?	Outcome [+]	Related to Treatment?
Placebo				
379 8/M/W/29	Femur fracture NOS [‡]	Yes	Recovered	No
654 6/F/W/21	Pyelonephritis NOS [‡]	Yes	Recovered	Yes
Tolterodine PR 2 mg q.d.				
105 7/F/W/25	Visual acuity reduced [‡]	No	Not recovered	No
112 8/M/W/27	Head injury [‡]	No [§]	Recovered	No
334 7/F/W/19	Pyrexia	No	Recovered	No
583 8/F/W/23	Pyelonephritis NOS [‡]	No [§]	Recovered	No

[*] Race abbreviations include: W = white.

[+] At follow-up after end of study treatment.

[‡] Adverse event was severe.

§ Study drug was temporarily withdrawn.

Source: Table 9-29, *5.3.5.1.1, p 93*

Medical Reviewer's Comment:

Subject 334 is listed as an SAE for pyrexia; however, the investigator's term is "Fever backpain + hospitalization APN suspect" – presumably referring to acute pyelonephritis

13.8.4 Frequent adverse events

At least one adverse event was reported by 54 and 57% of the tolterodine and placebo groups, respectively. The most frequent adverse events in the treatment group were headache, abdominal pain, nasopharyngitis, UTI, fever, diarrhea and vomiting. The most frequent events in the placebo group were headache, nasopharyngitis, cough and fatigue. Events occurring in the tolterodine group at twice the placebo rate were:

- Abdominal pain NOS (6.8 vs. 2.8%)
- UTI (4.3 vs. 1.9%)

- Abdominal pain, upper (3.8 vs. 1.9%)
- Fever (3.8 vs. 1.9%)
- Diarrhea (3.4 vs. 0.9%)
- Abnormal behavior (1.7 vs. 0%)

Regarding anticholinergic side effects, dry mouth/throat was reported in 1.7% of the treatment group, compared to 2.8% of the placebo group. Dry eyes were reported in 0.9% of tolterodine subjects and no placebo subjects. Constipation occurred in 1.7 vs. 0.9% of treatment and control subjects, respectively. There were no reported cases of frank urinary retention, but urinary difficulty occurred in 1.7% of subjects on tolterodine and 0.9% of placebo subjects. Thus, overall, the rate of common anticholinergic side effects was 6% in the tolterodine group and 4.6% in the placebo group.

Table 67 presents the adverse events occurring in ≥1% of subjects. Table 68 displays the incidence of adverse events by MedDRA System Organ Class. Broken down by age, the overall prevalence of adverse events was similar between placebo and treatment groups at the two younger age groups (4-6 year olds[6]: 55.9% in placebo, 55.6% in tolterodine; 7-8 year olds: 61.0% in placebo, 61.6% in tolterodine), and lower in the treatment group in the 9-11 year old groups (40.6% vs. 53.1% in placebo). The same pattern was seen when subdivided by weight: similar rates in the two smaller groups (61.1% in placebo vs. 64.3% for tolterodine in subjects under 20 kg; 54.8% for placebo vs. 58.9% for tolterodine in subjects weighing >=20 kg to 30 kg), and lower rates in the tolterodine group in the larger size groups (42.3% vs. 59.3% in the placebo group).

Medical Reviewer's comments:

1) **As this trial did not use weight-based dosing, the decreased incidence of adverse events in the tolterodine group with increasing body weight may indicate that adverse events are associated with drug exposure.**
2) **Some event counts in Table 67, which is from the study report, do not concur with those obtained by the reviewer after evaluating line listings for adverse events. For example, "cystitis" was coded separately from UTI, and the 3 tolterodine-treated and 1 placebo-subjects who experienced cystitis are not included in Table 67. Similarly, "aggressive behavior" was coded separately from "abnormal behavior," and is not listed in Table 67.**

Table 67 Adverse Events Reported by ≥1% of Subjects, by Treatment Group

System Organ Class	Adverse Event (preferred term)	Treatment Group			
		Placebo (n = 107)		Tolterodine PR 2 mg q.d. (n = 235)	
		N	%	N	%
Gastrointestinal Disorders	Abdominal pain NOS	3	2.8	16	6.8
	Abdominal pain upper	2	1.9	9	3.8
	Constipation	1	0.9	4	1.7
	Diarrhea NOS	1	0.9	8	3.4
	Dry mouth	3	2.8	3	1.3
	Nausea	3	2.8	6	2.6
	Sore throat NOS	3	2.8	2	0.9
	Vomiting NOS	2	1.9	8	3.4
General disorders and administration site Conditions	Fatigue	4	3.7	2	0.9
	Influenza like illness	1	0.9	3	1.3
	Pyrexia	2	1.9	9	3.8
Infections and Infestations	Gastroenteritis NOS	2	1.9	2	0.9
	Influenza	2	1.9	2	0.9
	Nasopharyngitis	8	7.5	11	4.7
	Upper respiratory tract infection NOS	3	2.8	2	0.9
	Urinary tract infection NOS	2	1.9	10	4.3
Musculoskeletal, connective tissue, and bone disorders	Arthralgia	2	1.9	2	0.9
Nervous system disorders	Dizziness (exc. vertigo)	3	2.8	3	1.3
	Headache NOS	15	14.0	24	10.2
Psychiatric disorders	Abnormal behavior NOS	0	0.0	4	1.7
Renal and urinary Disorders	Difficulty in micturition	1	0.9	4	1.7
	Urinary incontinence aggravated	2	1.9	1	0.4
Respiratory, thoracic and mediastinal Disorders	Cough	7	6.5	4	1.7
	Epistaxis	1	0.9	4	1.7
	Rhinitis NOS	1	0.9	3	1.3
Skin and subcutaneous tissue disorders	Dermatitis NOS	1	0.9	4	1.7
	Eczema NOS	2	1.9	0	0
Subjects reporting at least one AE		61	57.0	127	54.0
Total number of events		117	NA	239	NA

* For each subject, an event was counted only once regardless of the number of times reported.

Source: Table 9-25, *5.3.5.1.1 p 89*

Table 68 Adverse Events by MedDRA Organ System

System Organ Class	Treatment Group			
	Placebo (n = 107)		Tolterodine PR 2 mg q.d. (n = 235)	
	N	%	N	%
Blood and lymphatic system disorders	1	0.9	0	0.0
Cardiac disorders	0	0.0	1	0.4
Ear and labyrinth disorders	1	0.9	3	1.3
Eye disorders	2	1.9	3	1.3
Gastrointestinal disorders	19	17.8	53	22.6
General disorders and administration site conditions	9	8.4	13	5.5
Infections and infestations	24	22.4	50	21.3
Injury and poisoning	4	3.7	6	2.6
Investigations	1	0.9	2	0.9
Metabolism and nutrition disorders	0	0.0	1	0.4
Musculoskeletal, connective tissue, and bone disorders	3	2.8	3	1.3
Nervous system disorders	18	16.8	27	11.5
Psychiatric disorders	1	0.9	14	6.0
Renal and urinary disorders	5	4.7	7	3.0
Respiratory, thoracic, and mediastinal disorders	10	9.3	15	6.4
Skin and subcutaneous tissue disorders	3	2.8	7	3.0
Surgical and medical procedures	1	0.9	0	0.0
Vascular disorders	1	0.9	3	1.3
Subjects reporting at least one AE	61	57.0	127	54.0
Total number of events	117	NA	239	NA

Subjects with more than one adverse event in any system organ class were counted once for that system organ class.

For each subject, any event was counted only once (by preferred term) regardless of the number of times reported.

Source: Table 9-27, *5.3.5.1.1 p91*

Medical Reviewer's comments:

1) **Viewed by individual common adverse events, there are potentially concerning signals of elevated rates of UTI (4.3 vs. 1.9%) and abnormal behavior (1.7 vs. 0%) in the tolterodine group.**
2) **Viewed by body system, it is apparent that there is a higher incidence of psychiatric disorders in the treatment group: 14 cases (6%) vs. 1 (09%).**

Looking further into the psychiatric complaints, details of the 15 cases are:

- #246 (placebo) – 10 year old male who experienced moderate stress symptoms at an unknown time in the trial, judged unrelated to treatment, and recovered
- #105 – 7 year old female who experienced 63 days of mild irritability beginning on day 2, judged unrelated to treatment, and recovered
- #221 – 10 year old female who experienced 81 days of mild personality change beginning on day 12, judged unrelated to treatment, and recovered
- #282 – 6 year old female who experienced mild nervousness of unknown duration beginning on day 28. Symptoms were judged related to treatment and subject had not recovered at the end of observation.

- #293 – 8 year old male who experienced mild emotional disturbance of unknown duration beginning on day 68. Symptoms were judged related to treatment and subject had not recovered at the end of observation.
- #301 – 7 year old female who experienced encopresis of unknown duration beginning on day 56. Symptoms were judged related to treatment and subject had not recovered at the end of observation.
- #308 – 7 year old female who experienced 68 days of mild nightmares beginning on day 15, and 56 days of moderate abnormal behavior beginning on day 28, both judged related to treatment, and recovered
- #310 – 11 year old female who experienced severe mood alteration ("moodiness, bad temper" on CRF) of unknown duration beginning on day 6, and 39 days of severe aggression beginning on day 13. Symptoms were judged to be related to treatment; the aggression resolved with discontinuation of the drug, but the mood alteration remained unresolved at the end of observation.
- #316 – 10 year old male who experienced severe abnormal behavior at an unknown time in the trial, and 7 days of severe aggression beginning on day 41. Symptoms were judged to be related to treatment and resolved with discontinuation of the drug.
- #320 – 8 year old male with moderate tic and mild abnormal behavior occurring at an unknown time in the trial, judged to be treatment-related and not recovered at the end of observation
- #335 – 8 year old female who experienced severe encopresis of unknown duration beginning on day 49 and moderate attention deficit/hyperactivity disorder (ADHD) of unknown duration beginning on day 56. Encopresis was judged to be related to treatment, ADHD not related, and neither symptom had resolved by the end of observation.
- #479 – 7 year old male who experienced 15 days of moderate abnormal behavior beginning on day 21, judged to be unrelated, and recovered
- #495 – 10 year old female who experienced 9 days of mild irritability beginning on day 7, judged to be unrelated, and recovered
- #515 – 10 year old female who experienced 16 days of mild mood swings beginning on day 13, judged to be related to treatment, and recovered
- #660 – 7 year old female who experienced 69 days of moderate depression beginning on day 8, judged to be treatment-related and recovered following temporary drug withdrawal

These effects occurred in 9 females and 6 males, and 7 children aged 7 or younger and 8 children aged 8 or greater (however, 9 of 15 cases occurred in 7-8 year olds). Twenty individual events occurred in these 15 subjects; 4 had unknown time of onset, 11 occurred in the first four weeks of treatment, five from four to eight weeks of treatment and 1 after the eighth week of treatment.

13.8.5 Laboratory Values and Urinalysis

The serum chemistry, hematology, and urinalysis test results were reviewed. Shifts from baseline in laboratory parameters are presented in Table 69. The changes are generally not clinically significant.

Table 69 Shifts from Baseline in Laboratory Safety Variables

Clinical Laboratory Test	Treatment Group					
	Placebo (n = 107)			Tolterodine PR 2 mg q.d. (n = 235)		
	Up*	Down†	Missing‡	Up*	Down†	Missing‡
Erythrocytes	1	1	35	2	0	57
Hemoglobin	1	2	35	1	6	56
Platelets	3	0	35	0	1	59
Bilirubin, total	0	3	23	0	1	40
Alkaline phosphatase	2	0	23	2	0	38
Aspartate aminotransferase	0	1	23	1	2	38
Alanine aminotransferase	0	0	23	1	0	38
Creatinine	0	0	23	0	0	38
Thyroid-stimulating hormone	4	0	25	1	1	42
Sodium	2	0	23	4	0	38
Potassium	1	0	23	2	0	39

* Number of shifts from within or below the reference range at baseline to above the upper limit for the reference range at week 12 or at last visit.

† Number of shifts from within or above the reference range at baseline to below the lower limit for the reference range at week 12 or at last visit.

‡ Four additional subjects in the tolterodine group had no laboratory test results at any visit.

Source: Table 13-34, *5.3.5.1.1, p 146*

Urinalysis data showed that 2 subjects from each group experienced UTIs at week 12. Individual dipstick variables were rarely abnormal and changed little from baseline to the end of study.

Medical Reviewer's comment:

Up to approximately one-third of the placebo group and one-quarter of the tolterodine group were missing laboratory safety data.

13.8.6 Post Void Residual Urine Volume (PVR)

PVR was assessed at baseline and at Visits 3 and 4 and changed very little over the course of the study in either group. The increase in PVR appears to be slightly greater in the tolterodine group, but is unlikely to be of clinical significance. At week 12, mean PVR increased from baseline by 1.4 ml in the tolterodine group and decreased by 2 ml in the placebo group. Table 70 presents shifts in PVR over time by treatment group. 2.1% of tolterodine subjects, as compared to 0.9% of placebo subjects, had a PVR >=20% of theoretical capacity at the end of the study.

Table 70 Shift in PVR (% of Theoretical Bladder Capacity) by Treatment Group

Post-baseline Visit / PVR Urine Volume (% of theoretical bladder capacity) *	Treatment Group			
	Placebo (n = 107)		Tolterodine PR 2 mg q.d. (n = 235)	
	Baseline PVR *		Baseline PVR *	
	< 20% n (%)	≥ 20% n (%)	< 20% n (%)	≥ 20% n (%)
Week 4				
< 20%	106 (99.1)	1 (0.9)	230 (97.9)	3 (1.3)
≥ 20%	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Week 12				
< 20%	105 (98.1)	1 (0.9)	227 (96.6)	3 (1.3)
≥ 20%	1 (0.9)	0 (0.0)	5 (2.1)	0 (0.0)

* Based on the minimum value for each subject at each visit.

Source: Table 13-38, *5.3.5.1.1, p 149*

Medical Reviewer's comment:

The rationale for reporting PVR based on the minimal, rather than maximal, value obtained during each visit is not provided. Subjects were scanned a second time only if the first value were elevated (>= 20% theoretical capacity), thus using only the lower score may misclassify some subjects who actually did have an elevated PVR.

13.8.7 ECGs

One placebo subject and four tolterodine subjects had baseline ECGs classified as abnormal and clinically relevant. An additional six subjects in the tolterodine arm had abnormal but not clinically relevant ECGs at baseline. At week 12, one placebo subject had an abnormal but not clinically relevant ECG (with abnormal baseline ECG). Four tolterodine subjects with normal baseline ECGs had abnormal but not clinically relevant readings at 12 weeks. The single subject with a baseline clinically relevant abnormal ECG persisted in this finding (an ectopic atrial rhythm) at 12 weeks. Table 71 displays these data in more detail.

Table 71 Baseline and 12 Week ECGs by Treatment Group

ECG Result at Baseline	ECG Result at Week 12								
	Treatment Group								
	Placebo (n=107)				Tolterodine PR 2 mg q.d. (n=235)				
	Missing	Normal	Abnormal, not clinically relevant	Unable to evaluate	Missing	Normal	Abnormal, not clinically relevant	Abnormal, clinically relevant	Unable to evaluate
Missing	0	1	0	0	0	2	0	0	0
Normal	18	84	2	1	13	200	4	0	3
Abnormal, not clinically relevant	0	0	0	0	0	6	0	0	0
Abnormal, clinically relevant	0	1	0	0	0	3	0	1	0
Unable to evaluate	0	0	0	0	1	1	0	0	0

ECG = electrocardiogram; PR = prolonged release; q.d. = once daily.

Source: Table 13-41, *5.3.5.1.1, p. 152*

Minimal changes in QT interval were seen from baseline to 12 week assessments, either in standard QT interval or corrected interval, using the Bazett or Fridericia corrections. The small mean increases seen tended to be greater in the placebo group. Table 72 shows the frequency of QT interval changes

by 30 and 60 msec in the two groups. Again, using either correction , prolongation of QT interval by 30 or more msec occurred with higher frequency in the placebo group.

Table 72 Frequency of Change from Baseline QT Interval by Treatment Group

Change from Baseline in QTc	Treatment Group	
	Placebo (n = 89) n (%)	Tolterodine PR 2 mg q.d. (n = 220) n (%)
QTcB *		
Increase ≥ 60 msec	2 (2.2)	1 (0.5)
Increase ≥ 30 and < 60 msec	9 (10.1)	12 (5.5)
Decrease ≥ 60 msec	1 (1.1)	0 (0.0)
Decrease ≥ 30 and < 60 msec	9 (10.1)	20 (9.1)
QTcF †		
Increase ≥ 60 msec	1 (1.1)	0 (0.0)
Increase ≥ 30 and < 60 msec	5 (5.6)	9 (4.1)
Decrease ≥ 60 msec	0 (0.0)	0 (0.0)
Decrease ≥ 30 and < 60 msec	5 (5.6)	11 (5.0)

* QT interval corrected for heart rate according to Bazett = QT interval / [60/heart rate]$^{1/2}$.

† QT interval corrected for heart rate according to Fridericia = QT interval / [60/heart rate]$^{1/3}$.

Source: Table 13-40, *5.3.5.1.1, p 151*

Medical Reviewer's Comment:

Data summarizing mean or median QT interval are not reported; only change data are reported. The number of subjects in each group with intervals exceeding 450 msec is not reported. Unlike Studies 001 to 003, the presentation of the data does not allow easy identification of subjects with abnormal rhythms or QT intervals.

13.8.8 Vital Signs

Vital signs were not collected after the run-in (Visit 1) and therefore were not assessed as safety variables.

13.9 Reviewer's assessment of efficacy and safety

The primary efficacy endpoint, change from baseline to week 12 in number of weekly incontinence episodes, was not significant as compared to placebo. Significant differences from baseline as compared to the placebo group were also not demonstrated in the quantitative secondary endpoints, number of gross incontinence episodes, number of micturitions/24 hours and well-being assessed by the VASC. The subjective endpoint, parental perception of treatment benefit, did show a significant difference between treatment and placebo groups at 12 weeks; however, examination of the three possible responses on this question suggest that the proportion of treatment benefit rated as "much benefit" (as opposed to "little benefit") did not differ between the treatment and placebo groups.

Subgroup analyses were conducted to explore the effect of baseline frequency of micturition on response to treatment. When evaluated in this manner, subjects with "pathological frequency" (i.e., those with more than seven micturitions in 24 hours) did show significant improvement in number of weekly incontinence episodes and a significant increase in the urinary volume per micturition in subjects receiving tolterodine as compared to placebo. Further subgroup analyses suggest a benefit

to tolterodine in reduction of weekly incontinence episodes among children aged 4-6 years and among males.

Overall, there is no evidence of efficacy of tolterodine in reducing incontinence among children aged 5 to 10 years with symptoms of urinary urgency and frequency suggestive of detrusor instability.

There were no deaths and few serious adverse events in this study. The overall frequency of adverse events was similar between placebo and tolterodine treated subjects. The rate of anticholinergic side effects was slightly higher in the tolterodine group, but overall, was low in both groups. Laboratory and ECG data show no worrisome trends.

There were, however, concerning signals regarding increased incidence of urinary tract infections and behavioral disorders in the tolterodine group. The incidence of UTI was more than doubled (4.3 vs. 1.9% by the sponsor's categorization, which excludes cystitis and pyelonephritis) in the tolterodine group, which may be related to the doubling in the incidence of PVR over 20% of theoretical bladder capacity in this group. A number of psychiatric/behavioral complaints were reported in the tolterodine group, including two cases of aggressive behavior that led to study withdrawal.

14 CLINICAL TRIAL DETAPE-0581-008

14.1 Summary

Title: "A Phase III, Randomized, Double Blind, Multicenter and Multinational Study to Determine the Efficacy and Safety to Tolterodine Prolonged Release Capsules in Children 5 to 10 Years of Age with Symptoms of Urge Urinary Incontinence, Suggestive of Detrusor Instability" dated June 10, 2003.

There were no amendments made to Study 008.

First patient entered: April 9, 2002

Last patient completed: October 25, 2002

14.2 Objectives

The primary objective of this study was:

- to compare the clinical efficacy of tolterodine PR 2 mg daily with placebo in reducing the number of weekly daytime incontinence episodes after 12 weeks of treatment in children with symptoms of urinary urge incontinence suggestive of detrusor instability.

The secondary objectives were:

- to compare the clinical efficacy of tolterodine PR with placebo in reducing the number of weekly daytime incontinence episodes after four weeks of treatment, the number of micturitions/day, and the number of nights with nocturnal enuresis
- to compare the clinical efficacy of tolterodine PR with placebo in increasing urinary volume/void, and parent-assessment of quality of life and treatment benefit.
- to compare safety and tolerability of tolterodine PR with placebo
- to obtain population PK/PD data describing each subject's exposure to tolterodine and DD 01, the exposure-response relationship of tolterodine, DD 01 and the active moiety
- to evaluate the interaction of demographic factors and other covariates on PD and to explore the association of exposure and occurrence of adverse events

14.3 Overall Design

This Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled 12-week treatment duration, study was designed to evaluate the clinical efficacy and safety of tolterodine PR daily in 369 pediatric subjects aged 5 to 10 years, inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability. Subjects were randomized to tolterodine or placebo in a 2:1 ratio. Eligible subjects went through a one-week wash out from their current medication (if any) and a one-week run-in period. Efficacy data were collected based upon a micturition chart completed over 7 days prior to the baseline visit and each subsequent study visit (which followed four and 12 weeks of treatment), and upon a quality of life questionnaire completed at baseline and twelve weeks if treatment. Upon completion of the study, subjects were eligible to enter a 12-month open label safety extension study, or were followed for 1 week post-treatment.

The study was conducted at 49 sites in North America, Europe, Oceania and Asia (USA, Belgium, Denmark, Germany, Hong Kong, New Zealand, Russia, Slovakia, Slovenia, Sweden, and The Netherlands). The recruitment goal was 300 subjects, 200 to receive tolterodine, 100 to receive placebo, based on data obtained in Study 020.

14.4 Study Procedures and Conduct

14.4.1 Schedule of Study Assessments

During the wash-out/run-in Visit (Visit 1), informed consent and assent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after obtaining a medical history, vital signs, urinalysis and evaluation of post-void residual urine volume (PVR). Menstruating females were administered a urine pregnancy test. A micturition diary was given to potential subjects to assess ability to complete the diary as well as eligibility according to urinary frequency criteria. At the randomization visit (Visit 2), the quality of life questionnaire (PEMQoL) was administered, urinalysis and PVR were assessed again, subjects were randomized and micturition diaries and four weeks of medications were dispensed. Subjects were instructed to fill out the diaries in the 7 day period preceding the next study visit. All patients returned to the clinic for study assessments according to the schedule presented in Table 73. Urinalysis and PVR were evaluated at each visit, and serum sampling was done at Visit 3 to assess drug concentrations and for genotyping. At the final visit, vital signs were obtained, in addition to the urinalysis and PVR data.

Table 73 Schedule of Study Assessments

Part of study	Wash-out/ run-in	Inclusion	Treatment Period		Post-treatment
Visit	1	2	3	4	Telephone contact
Time in study (days)	−14 and −7[†]	0	21 – 35	77 – 91	+ 7
Written informed consent	X				
Demography	X				
Vital signs	X			X	
Study-specific medical history	X				
General medical history	X				
Urine dipstick test	X	X	X	X	
MSU for culture and microscopy	X	X[¶]	X[¶]	X	
Dipstick urine pregnancy test[#]	X				
PVR	X	X	X	X	
Blood sample (tolterodine and DD 01 metabolite, AAG/AGP, and CYP2D6/CYP3A[§] genotyping)			X		
Inclusion/ exclusion criteria	X	X			
Randomization		X			
Drug dispensing		X	X		
Compliance to treatment			X	X	
Dispensing of micturition diary[‡]	X	X	X		
Collection of micturition diary		X	X	X	
PEMQoL		X		X	
Treatment satisfaction questionnaire				X	
Concomitant medication	X	X	X	X	X
Adverse events			X	X	X

* Patients who did not continue into the open-label extension study (DETAPE-0581-009) had a follow-up telephone contact.
† Patients who had not received treatment for detrusor instability in the 7 days prior to Visit 1 could omit the 7-day wash-out period and directly enter the 7-day run-in period.
¶ Performed only if the urine dipstick test was positive for leukocytes.
\# Menstruating females only.
§ Genotyping for CYP3A and related haplotypes only for cases where the clinical phenotype was not explained by the core CYP2D6 panel. Samples taken at Hour 0 (pre-dose) and 4 - 6 hours post-dose.
‡ A micturition diary was dispensed at the screening visit to determine who could enter (both functionally from completing the micturition diary aspect as well as meeting the selection criteria). A micturition diary was dispensed at one visit to be completed during the 7 days immediately preceding the next scheduled visit.
** In addition to AE reporting at the post-treatment follow-up, any ongoing AEs were followed up again 1 week later, and all drug-related or serious AEs were followed until they resolved or were judged to be "stable" or "chronic."

Source: Table 1, *5.3.5.1.4, p 23*

14.5 Study Drug

14.5.1 Dose Selection

The drug studied was tolterodine prolonged release (PR) 2 mg capsules, taken once daily. The drug was to be taken daily in the morning and preferably swallowed whole with water. If a child were unable to swallow the capsule, it was allowed to be opened and the beads taken with food.

Medical Reviewer's comments:

1) **There is no description in the study report of the number of children unable to swallow capsules who therefore took the drug or placebo in bead form. Study 004 showed that these two methods of ingestion may not produce bioequivalence, as measured by Cmax. There is also no analysis evaluating differences in outcome according to method of ingestion.**
2) **The rationale for choosing the dose of 2 mg daily is not provided.**

14.5.2 Choice of Comparator

The study was placebo-controlled. Placebo was delivered in a capsule identical to the study drug.

14.5.3 Assignment to Study Drug

Subjects were randomized to tolterodine or placebo in a 2:1 ratio at Visit 2 by a random permuted block method with block size of 6. Study medication was prepackaged according to the randomization list and a multiple of the block size was delivered to each center. Double-blinding was maintained until closure of the database.

14.6 Patient Population

14.6.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or female, aged 5 to 10 years, inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability, defined by one or more episodes of incontinence daily during waking hours for at least 5 of 7 days AND mean urinary frequency of six or more micturitions per 24 hours, as confirmed by the run-in micturition chart

2. Participants/parents(s)/legal guardians(s) able to understand and cooperate with information given and who have provided written consent to participate in the study

3. Subjects who are able to swallow the capsules or to sprinkle the contents and consume the entire dose with food

4. Subjects who are able to complete the micturition diary

5. Female subjects of childbearing potential must be abstinent or using adequate contraception for three months prior to Visit 2 and throughout the study, and must have a negative urine pregnancy test at baseline

Exclusion Criteria

1. Any condition which, in the investigator's opinion, made the subject unsuitable for inclusion

2. Suspicion of a psychological component to the subject's incontinence

3. Nocturnal enuresis or "giggle incontinence" or overactive bladder of neurogenic origin

4. UTI at visit 1, a history of urinary retention, or PVR >= 20% of theoretical bladder capacity on at least 2 bladder scans at Visits 1 and 2

5. Known significant anatomic abnormalities of the urinary tract, significant anatomic or functional bladder outlet obstruction, symptoms of voiding dysfunction such as intermittent or staccato voiding, or history of surgery to the bladder neck or urethra

6. Severe constipation requiring rectal treatment and/or not responding to oral treatment

7. Recent history of significant hepatic or renal disease, uninvestigated hematuria or diabetes insipidus

8. An indwelling catheter or practicing clean intermittent catheterization

9. Participants taking any medications known to affect the lower urinary tract (except stable dose of desmopressin for nocturnal enuresis) or anticholinergic drugs or on an unstable dose of any drug with anticholinergic side effects

10. Treatment with any drug for detrusor instability or with electro-stimulation therapy or bladder training within 14 days of randomization

11. Any contraindications to or intolerance of anticholinergic therapy

12. Participants who have taken an investigation drug within a period of two months prior to study entry or who have previously participated in this study or Study 020

13. Participants with known allergy to tolterodine or its excipients

14. Treatment with potent CYP3A4 inhibitors

14.6.2 Demographics and Baseline Disease Characteristics

Forty-nine sites in eleven countries each enrolled 11 to 105 subjects. The US accounted for over one-fourth of the subjects. Subjects were distributed in an approximately 2:1 ratio between tolterodine and placebo within each country. Table 74 provides the breakdown by country for the 369 subjects in the Intention to Treat population (ITT). One subject did not take any study medication, and the safety population is therefore 368 subjects. The Per Protocol population (PP, N=269) excludes the 70 tolterodine and 30 placebo group major protocol violators.

Table 74 Subject Enrollment by Country

Country	Tolterodine PR 2 mg qd (N = 252)		Placebo (N = 117)	
	n	%	n	%
USA	73	29.0	32	27.4
Belgium	38	15.1	16	13.7
Denmark	26	10.3	13	11.1
Germany	8	3.2	4	3.4
Hong Kong	11	4.4	4	3.4
New Zealand	7	2.8	4	3.4
Netherlands	25	9.9	14	12.0
Russia	33	13.1	16	13.7
Slovakia	9	3.6	4	3.4
Slovenia	8	3.2	4	3.4
Sweden	14	5.6	6	5.1
Total	252	100.0	117	100.0

Source: Table T1.
Percentage (%) is based on total number of patients in ITT population treatment group.
Source: Table 2, *5.3.5.1.4, p 52*

Baseline demographic and baseline characteristics for the ITT population are summarized in Table 75 and Table 76. The trial enrolled a slight plurality of males. About 90% were Caucasian, with almost all the remaining subjects being Asian (4-6%) or Black (1-3%). The tolterodine group was very slightly older. Almost two-thirds of each group were extensive metabolizers by CYP2D6 genotyping, with the majority of the remainder being untested subjects. Median treatment group weight was 25.0 kg (range 15.9-83.5 kg), while median placebo group weight was 26.0 kg (range 15.5-69.3 kg). BMI, however, was almost identical between groups. Less than half of each group had received previous medical treatment for urinary urge incontinence, and of those who had, more placebo subjects had experienced good efficacy of this treatment. Treatment and placebo subjects were similar on baseline number of weekly incontinence episodes, mean number of micturitions/24 hours and mean volume per void.

Medical Reviewer's comments:

1) **The placebo group had a higher proportion of those subjects who had experienced good efficacy on previous medication therapy for urinary urge incontinence. This could result in unequal assignment of less likely responders to the treatment group.**
2) **It appears that 3-4% of subjects failed to meet inclusion criterion concerning number of daily incontinence episodes at baseline, and that 8% failed to meet the baseline urinary frequency criterion.**

Table 75 Demographic Characteristics of ITT Population

Demographic Characteristics		Tolterodine PR 2 mg qd N = 252	Placebo N = 117
		n (%)	n (%)
Gender	Male	128 (50.8)	65 (55.6)
	Female	124 (49.2)	52 (44.4)
Age group (years)			
	4 – 6	100 (39.7)	55 (47.0)
	7 – 8	106 (42.1)	40 (34.2)
	9 – 11	46 (18.3)	22 (18.8)
Race			
	White	225 (89.3)	108 (92.3)
	Black	7 (2.8)	1 (0.9)
	Asian	16 (6.3)	5 (4.3)
	Not listed	4 (1.6)	3 (2.6)
Age (years)	Mean (SD)	7.44 (1.54)	7.36 (1.49)
	Median	7.30	7.00
	(min – max)	(4.90 – 10.90)	(5.10 – 10.70)

Source: *Table 6, 5.3.5.1.4, p 57*

Table 76 Baseline Characteristics of ITT Population

Baseline Characteristics		Tolterodine PR 2 mg qd N = 252	Placebo N = 117
Weight (kg)	Mean (SD)	27.54 (10.13)	27.66 (8.78)
	Median (min – max)	25.00 (15.90 – 83.50)	26.00 (15.50 – 69.30)
Weight group (kg)	<20, n (%)	38 (15.1)	16 (13.7)
	≥20 – <30, n (%)	145 (57.5)	69 (59.0)
	≥30, n (%)	69 (27.4)	32 (27.4)
Height (cm)	Mean (SD)	125.12 (11.16)	125.44 (11.25)
	Median (min – max)	125.50 (94.00 – 155.20)	124.50 (96.00 – 151.00)
BMI (kg/m^2)	Mean (SD)	17.24 (3.94)	17.27 (3.26)
	Median (min – max)	16.20 (11.80 – 38.50)	16.30 (10.80 – 30.40)
EM/PM	Patients not reporting, n (%)	92 (36.5)	41 (35.0)
	EM, n (%)	155 (61.5)	72 (61.5)
	PM, n (%)	5 (2.0)	4 (3.4)

Previous Treatment for OAB		Tolterodine PR 2 mg qd N = 252	Placebo N = 117
Previous medical treatment for OAB	No, n (%)	150 (59.5)	73 (62.4)
	Yes, n (%)	102 (40.5)	44 (37.6)
Efficacy of previous medical treatment for OAB *	Poor, n (%)	54 (52.94)	20 (45.45)
	Good[†], n (%)	48 (47.06)	24 (54.55)
Previous non-medical treatment for OAB	No, n (%)	205 (81.3)	93 (79.5)
	Yes, n (%)	47 (18.7)	24 (20.5)
Efficacy of previous non-medical treatment for OAB*	Poor, n (%)	39 (82.98)	17 (70.83)
	Good[†], n (%)	8 (17.02)	7 (29.17)

Source: Table T6.
Percentage (%) is based on total number of patients in ITT population treatment group, except as noted in Footnote *. Data were available for all patients.
* Among patients who had previous treatment for OAB.
† Applies to those patients with good efficacy reported for ≥ one previous medication.
Source: Tables 7 & 8, *5.3.5.1.4, p 58*

14.6.3 Withdrawals, compliance, and protocol violations

Seventeen tolterodine and eight placebo subjects discontinued the trial early (Table 77), for a withdrawal rate of 6.8% in each group. Two and four subjects, respectively, in the placebo and tolterodine groups withdrew due to adverse events (see Section 14.8.3). Withdrawals due to lack of treatment efficacy were more frequent in the placebo group (2.6% vs. 0.8%), while loss to follow-up occurred more often in the tolterodine group (2.8% vs. 0%).

Table 77 Reasons for Withdrawal by Group

Reason for withdrawal	Tolterodine PR 2 mg qd (N = 251)		Placebo (N = 117)	
	n	%	n	%
Adverse event	4	1.6	2	1.7
Protocol violation	3	1.2	2	1.7
Consent withdrawn	1	0.4	1	0.9
Lost to follow-up	7	2.8	0	0
Lack of efficacy	2	0.8	3	2.6
Total	17	6.8	8	6.8

Source: Table 3, *5.3.5.1.4, p 53*

Rating of compliance was based on investigator assessment of 75% or greater compliance, as reflected in the comparison of expected number of capsules taken to amount of unused study medication returned at Visits 3 and 4. Compliance at week four was rated as 96% in the tolterodine group and 98% in placebo; at week 12, it was 92% in each group.

Medical Reviewer's comments:

1) **Although eleven tolterodine subjects are counted as non-compliant at week 12, *individual data listings* show 12 patients who were non-compliant at the end of treatment, including one (# 10075) described as a protocol violation who withdrew from the trial after approximately 4 weeks.**

2) **Three cases of non-compliance in the tolterodine group and one in the placebo group were attributed to ineffectiveness of the study drug. One case (#21064) of tolterodine noncompliance was attributed to an adverse event (a rash, for which the drug was withdrawn).**

Protocol violation criteria were defined a priori and subjects categorized as violators prior to unblinding. Major protocol violations occurred in 30 placebo subjects (26%) and in 70 treatment subjects (28%). Specific violations are noted in Table 78. The most common violations in both groups were occurrence of Visit 4 outside of the time limits (+/- 14 days of 12 weeks post-randomization), use of prohibited medications or noncompliance at Visit 4.

Table 78 Major Protocol Violations by Group

PP Exclusion criteria	Tolterodine PR 2 mg qd (N = 252)	Placebo (N = 117)
	n (%)	n (%)
Total number of (%) patients with major violation (s)	70 (27.8)	30 (25.6)
No complete diary for at least 4 days at Visits 2 and 4	17 (6.7)	6 (5.1)
Fewer than 5 incontinence episodes per 7 days at Visit 2	6 (2.4)	1 (0.9)
Mean urinary frequency ≤5.5 per 24h at Visit 2	10 (4.0)	3 (2.6)
Prohibited medication	29 (11.5)	11 (9.4)
Compliance <75% according to investigator's opinion at Visit 4	21 (8.3)	9 (7.7)
Visit 4 occurred outside ±14 days of 12 weeks after randomization visit	27 (10.7)	13 (11.1)
Violation of inclusion/exclusion criteria according to CRF	4 (1.6)	0 (0.0)
Confirmed PVR of at least 20% and patient not withdrawn from study	1 (0.4)	0 (0.0)
Age at baseline less than 4.5 years or more than 11.5 years	0 (0.0)	0 (0.0)

Source: Table T3.
A patient could have more than one violation. Percentage (%) is based on total number of patients in ITT population treatment group.

Source: Table 4, *5.3.5.1.4, p 54*

Medical reviewer comments:

1) **The number of subjects listed as noncompliant at Visit 4 in the above table is discordant with the data presented in the individual subject listings for compliance, where only 4 placebo and 12 tolterodine subjects were noted to be noncompliant. This may represent the inclusion of the four placebo and nine tolterodine subjects who had missing information, precluding assessment of compliance, among the subjects described as noncompliant.**

2) **The classification of subjects' compliance with the entry criteria concerning number of weekly incontinence episodes and daily frequency of micturition is not clear. The inclusion criteria specify that these should be evaluated from the diary dispensed at Visit 1 and returned at Visit 2. According to protocol violation classification, 6 tolterodine and 1 placebo subjects had too few incontinence episodes at Visit 2; however, the baseline data note that 10 tolterodine and four placebo subjects did not meet this criterion. Similarly, protocol violations occurred due to insufficient urinary frequency for 10 tolterodine and 3 placebo subjects; however, the baseline data show that 21 tolterodine and 10 placebo subjects failed to meet this criterion. An additional four tolterodine subjects are listed as protocol violators due to violation of inclusion/exclusion criteria (unspecified), but even adding these to the count, the number of protocol violations attributed to inclusion/exclusion violations would be 20 tolterodine subjects and four placebo subjects, while the baseline data suggest that 31 tolterodine subjects and fourteen placebo subjects actually violated inclusion/exclusion criteria. Inclusion of these additional subjects would raise the major protocol violation rate to 32% in the tolterodine group and to 34% in the placebo group.**

14.7 Efficacy

14.7.1 Key Efficacy Assessments

The primary efficacy endpoint was change from baseline in the number of weekly incontinence episodes occurring during daytime after twelve weeks of treatment. The secondary efficacy endpoints were change from baseline in:

- number of weekly incontinence episodes after four weeks of treatment
- mean number of daily micturitions after four and twelve weeks of treatment
- mean urinary volume per void after four and twelve weeks of treatment (recorded for 2 of the seven days assessed in each of the micturition diary periods)
- mean number of nights per week with nocturnal enuresis after four and twelve weeks of treatment

Additionally, the proportion of subjects fully continent at Visits 3 and 4 were calculated and compared, and the degree of improvement on the primary variable was categorized into four categories and compared across treatment groups. The clinical efficacy variables were based on the micturition diaries provided to subjects for recording seven day intervals preceding Visits 2 (baseline data), 3 (four week data) and 4 (12 week data). Data obtained during a period when the subject had a symptomatic UTI were excluded from the PP analysis, but included in the ITT analysis.

Parental assessment of the subject's and family's quality of life was also assessed, using the Pediatric Enuresis Module to Assess the Quality of Life (PEMQoL), given at visits 2 and 4. This instrument is a 43 item, 5-level Likert scale questionnaire developed to assess the impact of urinary incontinence on quality of life of children aged 5-17 years and their families. Responses are assessed over a four-week recall period and eight child and family subscales are scored independently on a 0-100 scale. Parents also completed a treatment satisfaction questionnaire rating satisfaction with treatment process and treatment outcome at week 12.

Additional analyses pre-specified in the protocol included subgroup analysis for age, race, weight and gender, and exploration of possible relationships between baseline characteristics and efficacy/safety variables and between baseline urinary volume and age, sex and micturition chart variables.

Medical reviewer comments:

1) **Although generally the micturition chart data were collected over 7 days, the volume/void was measured on only 2 of the 7 diary days. It is not specified which two days were chosen, whether they were consecutive and whether the choice of days was made by the subject/parent, by the investigator, or pre-specified in the protocol.**
2) **No information on reliability or validity of either the PEMQoL or the treatment satisfaction questionnaire is provided.**

14.7.2 Pharmacokinetic Assessments

Serum samples for pharmacokinetics were to be obtained at Visit 3 within 14-24 hours following the previous dose of study medication. The PK/PD objectives were:

- Estimation of each subject's exposure to tolterodine and DD 01
- Exploration of the exposure-response relationship of tolterodine, DD 01 and the active moiety and modeling of the exposure-response relationship of combined exposure to tolterodine and DD 01
- Evaluation of the effects of demographic factors on PD
- Exploration of the relationship between exposure and AE incidence

PK data from Study 008 was pooled with data from Study 020; the pooled analysis is discussed in Section 5.1.2.4.

14.7.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was change from baseline to week 12 in number of weekly incontinence episodes during waking hours. The analysis was conducted on the ITT population, with analysis of the PP population presented as supportive.

Data on reduction in the number of weekly incontinence episodes are shown in Table 79. Both tolterodine and placebo groups displayed decreasing frequency of incontinence with increasing time on treatment, with a slightly lower frequency occurring in the tolterodine group at both weeks 4 and 12. The comparison between groups in change from baseline at twelve weeks was not significant (p=0.4). Per protocol patient analyses were also performed, and statistical significance was not reached.

Table 79 Change in Weekly Incontinence Episodes

Number of Daytime Incontinence Episodes per Week		Tolterodine PR 2 mg qd (N = 252)	Placebo (N = 117)
Baseline	Mean (SD)	19.39 (13.31)	18.82 (14.07)
	Median (min – max)	16.00	14.00
	Patients not reporting (n)	1	0
Week 4	Mean (SD)	11.91 (12.71)	13.31 (12.94)
	Median (min – max)	8.00	11.00
	Patients not reporting (n)	0	0
Week 12	Mean (SD)	9.34 (11.78)	10.03 (10.06)
	Median (min – max)	5.00	7.00
	Patients not reporting (n)	0	0
Change from baseline to Week 12	Mean (SD)	−10.02 (12.15)	−8.79 (11.13)
	Median (min – max)	−9.00	−7.00
	Patients not reporting (n)	1	0
Difference vs. placebo after 12 weeks	Least Square Mean (SEM)	−0.88 (1.05)	
	95% CI	(−2.94, 1.18)	
	p-value	0.403	

Source: Table 14, *5.3.5.1.4, p 63*

Subgroup analyses showed significant differences between tolterodine and placebo when the 51 subjects weighing more than 35 kg were excluded from the analysis (p=0.05).

Medical Reviewer's comments:

1) **The ITT population analysis includes those 23 subjects noted in Table 71 to have at least four days of diary data missing at Visits 2 and 4.**
2) **The remainder of the subgroup analyses conducted are not described, nor are the number of such sub-analyses reported.**
3) **The validity of discarding almost 15% of the sample to do a subgroup analysis on lower weight subjects is questionable.**

14.7.4 Secondary Efficacy Endpoint Analysis

Secondary endpoints were mean change from baseline to week 4 in weekly number of daytime incontinence episodes, number of micturitions/24 hours at four and twelve weeks, urinary volume/void at four and twelve weeks, and frequency of nocturnal enuresis after four and twelve weeks, as well as parental responses on the PEMQoL and the treatment satisfaction questionnaire. Results on the secondary endpoints generally did not demonstrate an efficacy advantage in the treatment group.

The change in number of incontinence episodes from baseline to week 4 was not significantly different between placebo and treatment groups (p=0.09), nor was change in mean number of daily micturitions at either week 4 (p=0.23) or week 12 (p=0.72) nor change in frequency of nocturnal enuresis at week 4 (p = 0.05) or 12 (p=0.31). All five measures decreased with time in both groups. Similar results were obtained in the PP analysis. The mean volume per micturition increased over time, and did differ significantly between groups at both four weeks and twelve weeks (Table 80).

Table 80 Mean Urinary Volume per Micturition by Treatment Group

Mean Urinary Volume Voided per Micturition		Tolterodine PR 2 mg qd (N = 252)	Placebo (N = 117)
Baseline	Mean (SD)	85.29 (38.78)	84.73 (36.57)
	Median (min – max)	77.68	80.68
	Patients not reporting (n)	6	1
Week 4	Mean (SD)	98.62 (42.28)	91.42 (40.81)
	Median (min – max)	91.67	85.71
	Patients not reporting (n)	0	0
Week 12	Mean (SD)	104.84 (47.95)	95.06 (46.32)
	Median (min – max)	95.46	88.00
	Patients not reporting (n)	0	0
Change from Baseline to Week 4	Mean (SD)	12.49 (32.94)	5.92 (24.15)
	Median (min-max)	12.37 (	5.66
	Patients not reporting (n)	6	1
Difference vs Placebo after 4 weeks	Least Square Mean (SEM)	6.58 (3.29)	
	95% Confidence Interval	(0.10, 13.05)	
	P-value	0.047	
Change from baseline to Week 12	Mean (SD)	18.68 (40.13)	9.59 (27.40)
	Median (min – max)	13.23	5.43
	Patients not reporting (n)	6	1
Difference vs. placebo after 12 weeks	Least Square Mean (SEM)	9.16 (4.04)	
	95% CI	(1.22, 17.11)	
	p-value	0.024	

Source: Tables 18 & T44, *5.3.5.1.4, pp 67, 175*

A nonparametric analysis was also conducted of several of these variables, pre-specified to be a supportive, not primary analysis. Assessment of change from baseline to 12 weeks in number of incontinence episodes, number of daily micturitions, mean volume/void and frequency of nocturnal enuresis found significance only in the mean volume/void (p=0.002). The degree of improvement of incontinence at week 12 was evaluated both by chi-square, testing the proportion fully continent, and by Wilcoxon test, testing for the difference in assignment to the five improvement categories. Fifteen percent of the tolterodine group become fully continent, compared to 10% of the placebo group; this was not significantly different (p=0.12). The three "improved" categories contained a higher frequency of tolterodine subjects, while the "unimproved to worse" categories contained a higher frequency of placebo subjects (p=0.04).

None of the subscales on the PEMQoL showed a significant difference between treatment groups. Parental satisfaction with treatment assessed responses at the end of treatment to 10 questions. The tolterodine group was significantly superior to placebo on the measures involving change in overall quality of life (p=0.02), improvement in symptoms (p = 0.03) and satisfaction with outcome (p=0.005).

Medical Reviewer's comments:

1) **Correction for multiple comparisons on the nine secondary endpoints and on the various subscales within the parental response instruments was not done.**

2) **The sponsor reports that the change in frequency of nocturnal enuresis was not significant at either week 4 or 12; however, the data presented show a p-value of 0.049 at the four week comparison. Since this p value should be corrected for multiple comparisons, it would not, in fact, reach statistical significance. The statistics reviewer, in reanalyzing the sponsor's data, obtained a p-value of 0.07.**

3) **One of the subscales on the PEMQoL is described as "Treatment Success Scale." For reasons that are not given, the sample size for this subscale is significantly reduced as compared to the other subscales, in both tolterodine and placebo groups, with only about 57% of the subjects responding. The placebo group outscored the tolterodine group on this measure.**

14.7.5 Pharmacokinetic Data Summary

Pooled PK data were compiled for Studies 020 and 008 and are reviewed in Section 5.2

14.8 Safety

14.8.1 Safety Measurements

All participants who received at least one dose of study medication were to be included in the summaries and listings of safety data (one subject received no medication; thus, the safety population is 368). Adverse events were coded according to the Medical Dictionary for Regulatory Action (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events and reasons for withdrawal from the trial
- Post void residual urine volume (PVR), measured by bladder ultrasonography at each visit. A positive scan was defined as >=20% of the theoretical bladder capacity, computed by {60 + (30*age)].

Medical Reviewer's comment:

The theoretical bladder capacity was computed in Study 020 by a different formula: [30+(30*age)], with no reference given supporting this formula. As the two studies used populations of the same age, it is not clear why a different formula for calculating theoretical bladder capacity would be proposed.

14.8.2 Extent of exposure

Time in study for the tolterodine group is displayed in Table 81. There was a marked decrease in sample size in the last two weeks of the study.

Table 81 Treatment Duration in Tolterodine Group

Time on treatment (weeks)	Number of patients	%
>0	242	96.41
≥4	242	96.41
≥8	237	94.42
≥9	237	94.42
≥10	236	94.02
≥11	224	89.24
≥12	157	62.55
Unknown	9	3.59

Source: Table 11, *5.3.5.1.4, p 61*

The frequency with which subjects dosed by opening the capsule and sprinkling beads on food is reported in Table 82. Slightly more subjects were able to consume the capsule by the end of the study, and at both weeks 4 and 12, the tolterodine group had a slightly higher frequency of using the sprinkled beads.

Table 82 Method of Drug Administration by Treatment Group

Most common Method of Drug Administration		Tolterodine PR 2 mg qd (N = 252)		Placebo (N = 117)	
		n	%	n	%
Week 4	Whole capsule	210	83.3	103	88.0
	Sprinkled beads	34	13.5	13	11.1
	Not reported	8	3.2	1	0.9
Week 12	Whole capsule	214	84.9	102	87.2
	Sprinkled beads	36	14.3	12	10.3
	Not reported	2	0.8	3	2.6

Source: Table 12, *5.3.5.1.4, p 61*

Medical Reviewer's comments:

1) ***Given that*** **Table *81* is based on the safety population (excluding the one subject who took no study medication), it is unclear why an additional nine tolterodine subjects are missing as early as ">0 weeks" of treatment or how they could remain in the safety population if in fact they left the study before completing more than 0 weeks of treatment.**
2) **The reason for the considerable drop in participation at week 12 is not provided. Given that Visit 4 could occur within +/- 7 days of the expected date, the 67 subjects in the tolterodine treatment who apparently withdrew between 11 and 12 weeks may represent study who had their Study 4 visit on days 77-83.**
3) **No data are provided regarding the treatment duration in the placebo group.**
4) **Although the use of sprinkled beads appears similar in the two groups as presented in Table 82, this obscures the actual pattern of use, which is presented *in* Table *83*, generated by the reviewer from the raw data. More than four times as many tolterodine as placebo subjects used the beads throughout the study; placebo subjects more commonly used the beads in the early part of the study and were able to consume the capsules by the latter part of the study.**

Table 83 Method of Drug Administration over Portions of the Study by Treatment Group

Time	Method	Tolterodine: N	%	Placebo N	%
At week 4 assessment only	Whole capsule	243	96.4	107	91.5
	Sprinkled beads	3	1.2	9	7.7
	Not reported	6	2.4	1	0.9
At week 12 assessment only	Whole capsule	245	97.2	110	94.0
	Sprinkled beads	5	2.0	4	3.4
	Not reported	2	0.8	3	2.6
Throughout study	Whole capsule	220	87.3	114	97.4
	Sprinkled beads	31	12.3	3	2.6
	Not reported	1	0.4	0	0

Source: Appendix 3.5.2, *5.3.5.1.4, pp 925-981*

5) No analysis of outcome is made considering method of drug administration (intact capsule v. sprinkled beads).

14.8.3 Serious adverse events

Deaths: there were no deaths.

Premature termination due to safety reasons: Two placebo and four tolterodine subjects terminated prematurely from the study because of adverse events. They are listed in Table 84. The two subjects in the placebo group suffered four adverse events, one mild and two moderate, all of which were judged to be treatment-related (dermatitis in one subject and a combination of events beginning on day 1 and described as micturition urgency, difficulty in micturition and daytime enuresis). Six adverse effects occurred in the four tolterodine-treated subjects, five mild and one moderate. All were judged to be treatment related. Adverse events leading to withdrawal were difficulty in micturition in two subjects (described as more residual volume and PVR >20% of bladder capacity, respectively), abnormal behavior ("insubordination") in one and one child developed rash, abdominal pain and decreased appetite. The adverse events that occurred in the placebo group occurred in the first 1-2 days, while those in the tolterodine group were uncharacterized as to onset in four cases, and occurred after about four weeks of treatment in the other two cases.

Table 84 Withdrawals due to Adverse Events

Treatment	Investigator/ Patient	Age (y)/ Race/ Gender/ Weight (kg)	Investigator Term	Preferred Term (MedDRA)	Onset Day/ Duration (days)	AE max seriousness/ intensity	Outcome of AE	AE related?/ Drug withdrawn?
Placebo								
	41592/25029	9/W/M/36	Skin rash	Dermatitis NOS	2/6	No/Moderate	Recovered	Yes/Yes
	47827/20079	7/W/M/20	More urge syndrome (urgent micturition)	Micturition urgency	1/30	No/Moderate	Not recovered	Yes/Yes
	47827/20079	7/W/M/20	More residual volume (more urinary retention) (difficulty in micturition)	Difficulty in micturition	1/30	No/Moderate	Not recovered	Yes/Yes
	47827/20079	7/W/M/20	Enuresis (diurnal)	Enuresis	1/30	No/Mild	Not recovered	Yes/Yes
Treatment	Investigator/ Patient	Age (y)/ Race/ Gender/ Weight (kg)	Investigator Term	Preferred Term (MedDRA)	Onset Day/ Duration (days)	AE max seriousness/ intensity	Outcome of AE	AE related?/ Drug withdrawn?
Tolterodine PR 2 mg qd								
	39718/21020	7/W/M/36	Insubordination behavior abnormal	Abnormal behavior NOS	/21	No/Moderate	Unknown	Yes/Yes
	50933/10074	10/W/F/27	Difficulty in micturition (More residual volume)	Difficulty in micturition	28/41	No/Mild	Recovered	Yes/Yes
	57296/21060	5/W/F/20	PVR >20% of theoretical bladder capacity (difficulty in micturition)	Difficulty in micturition	32/39	No/Mild	Not recovered	Yes/Yes
	57296/21064	5/W/F/21	Rash	Rash erythematous	/16	No/Mild	Recovered	Yes/Yes
	57296/21064	5/W/F/21	Abdominalia	Abdominal pain NOS	/6	No/Mild	Recovered	Yes/Yes
	57296/21064	5/W/F/21	Appetite poor	Appetite decreased NOS	/33	No/Mild	Not recovered	Yes/Yes

Source: Table 35, *5.3.5.1.4, p 102-103*

Medical Review Comment:

The placebo subject who was withdrawn due to micturition difficulty and "more residual volume" did not actually have an elevated PVR.

Serious adverse events: There were two tolterodine subjects who experienced three serious adverse events (SAEs). They are listed in Table 85. No SAEs occurred in the placebo group. None of the SAEs resulted in withdrawal (although one did require temporary discontinuation of the drug during hospitalization), and none were considered treatment related. Details of the cases are:

- #10202 – hospitalized with fever and UTI, treated with 14 days of antibiotics; drug was restarted three days after diagnosis and patient was placed on UTI prophylaxis for the remainder of the study
- #21008 – developed an abscess behind the right knee which required hospitalization and incision and drainage; the infection recurred about two weeks later, and required a second course of antibiotics to resolve

Table 85 Serious Adverse Events

Treatment	Investigator	Patient	Age (y)/ Race/ Gender/ Weight (kg)	Investigator Term	Preferred Term (MedDRA)	Onset Day/ Duration (days)	AE max intensity	Outcome of AE	Action Taken	Related to Study Drug?
Tolterodine PR 2 mg qd										
	39717	21008	7/W/F/21	Small infection behind right knee (abscess)	Abscess NOS	35/26	Moderate	Recovered	None	No
	55643	10202	6/W/F/28	Urinary tract infection	Urinary tract infection NOS	59/7	Moderate	Recovered	Dose Delayed/ Changed	No
	55643	10202	6/W/F/28	Fever	Pyrexia	59/7	Moderate	Recovered	Dose Delayed/ Changed	No

Source: Table T10

Source: Table 34, *5.3.5.1.4, p 100*

Medical Reviewer's comment:

Although subject 10202 is described as having a UTI, the details of her hospitalization and duration of antibiotics suggest that it may have been pyelonephritis. Justification of the determination that this SAE was unrelated to the treatment is not given.

Frequent adverse events: At least one adverse event was reported by 64 and 62% of the tolterodine (N=161) and placebo groups (N=73), respectively. The most frequent adverse events were UTIs, headaches and fever. Events occurring in the tolterodine group at twice the placebo rate were:

- Eye irritation (0.8 vs. 0%)
- Pneumonia (0.8 vs. 0%)
- Decreased appetite NOS (0.8 vs. 0%)
- Rhinitis NOS (2.0 vs. 0%)
- Diarrhea (3.2 vs. 0.9%)
- Constipation (2.4 vs. 0.9%)
- Headache NOS (4.4 vs. 1.7 %)

Regarding anticholinergic side effects, dry mouth was reported in one subject in each group, or 0.4% of the treatment group, compared to 0.9% of the placebo group. Dry eyes or blurred vision were reported in 0.8% of tolterodine subjects and no placebo subjects. Constipation occurred in 2.4 vs. 0.9% of treatment and control subjects, respectively. There were no reported cases of frank urinary retention, but urinary difficulty occurred in 1.2% of subjects on tolterodine and 1.7% of placebo subjects.

Table 86 presents the adverse events occurring in ≥2% of subjects. Adverse event rates were also analyzed by gender, age group, weight group and most common method of administration. Stratified by gender, it is clear that females experienced a higher frequency of adverse events in both the tolterodine (89.5% vs. 60%) and placebo groups (86.5% vs. 63.1%). The most striking discrepancy was the incidence of UTI: 16.9% among tolterodine treated girls as compared to 1.6% in males, and 11.5% in placebo treated girls as compared to 0% in males. Table 87 shows the incidence of adverse events by age and treatment group and by weight and treatment group. Younger children had a higher frequency of adverse events in both tolterodine and placebo groups. Adverse events were higher in the lowest weight group within the tolterodine arm, consistent with an exposure-effect

relationship, but this pattern was not seen in the middle weight group, who had a lower frequency of adverse events than the heaviest children.

The study reports that safety and tolerability did not differ according to the method of administration of the study drug (intact capsule vs. sprinkled beads). Table 88 was created by the reviewer, and shows the distribution of adverse events by treatment group and method of administration, at both the four week visit and the twelve week visit.

Table 86 Adverse Events Reported by ≥2% of Subjects, by Treatment Group

System Organ Class/Adverse Event (preferred term)		Tolterodine PR 2 mg qd N=251		Placebo N=117	
		n	%	n	%
Gastrointestinal disorders	Abdominal pain NOS	6	2.4	4	3.4
	Abdominal pain upper	6	2.4	5	4.3
	Constipation	6	2.4	1	0.9
	Diarrhea NOS	8	3.2	1	0.9
	Sore throat NOS	4	1.6	3	2.6
	Vomiting NOS	9	3.6	3	2.6
General disorders and administration site conditions	Pyrexia	9	3.6	8	6.8
Infections and infestations	Influenza	1	0.4	3	2.6
	Nasopharyngitis	7	2.8	3	2.6
	Urinary tract infection NOS	23	9.2	6	5.1
Nervous system disorders	Headache NOS	11	4.4	2	1.7
Respiratory, thoracic and mediastinal disorders	Cough	8	3.2	3	2.6

Source: Table T17.
Percentage (%) is based on total number of patients in the safety population for each treatment group. For each patient, an event was counted only once regardless of the number of times reported.

Source: Table 30, *5.3.5.1.4, p 90*

***Table 87* Adverse Events by Age, Weight and Treatment Groups**

	Tolterodine Groups			Placebo Groups		
All Adverse Events	4-6 years N = 100	7-8 years N = 105	9-11 years N = 46	4-6 years N = 55	7-8 years N = 40	9-11 years N = 22
N	86	82	19	52	26	8
%	86.0	78.1	41.3	94.5	65.0	36.4
All Adverse Events	< 20 kg N = 38	>=20 & <30 N = 145	>= 30 kg N = 68	< 20 kg N = 16	>=20 & <30 N = 69	>= 30 kg N = 32
N	40	94	53	8	59	19
%	105.3	64.8	77.9	50.0	85.5	59.4

Source: Tables T67 & T68, *5.3.5.1.4, pp 229-228*

Table 88 Adverse Events by Method of Administration and Treatment Group

	Tolterodine Groups		Placebo Groups	
All Adverse Events – 1st 4 Weeks	Whole Capsule N = 210	Sprinkled Beads N = 34	Whole Capsule N = 103	Sprinkled Beads N = 13
N	60	24	36	5
%	28.6	70.6	35.0	38.5
All Adverse Events – Wks 5-12	Whole Capsule N = 214	Sprinkled Beads N = 36	Whole Capsule N = 102	Sprinkled Beads N = 12
N	43	20	21	4
%	20.1	55.6	20.6	33.3

Source: Tables T69 & T70, *5.3.5.1.4, pp 217-235*

Medical Reviewer's comments:

1) **The total number of subjects experiencing adverse events in each group is not reported, but must be calculated from the listings of individual categories.**
2) **Although occurring at less than twice the placebo rate, two events having increased incidence in the tolterodine group are worth noting: UTIs, including cystitis and pyelonephritis (7.6% in the tolterodine group vs. 5.1% in the placebo group) and abnormal/aggressive behavior (1.6% in the tolterodine group vs. 0.9% in the placebo group).**
3) **The sponsor counts twenty-four events (classed under eye disorders, gastrointestinal disorders, general disorders, psychiatric disorders and renal and urinary disorders) as anticholinergic adverse events. Using the sponsor's classification, 54 tolterodine subjects, or 21%, and 27 placebo subjects, or 23%, experienced anticholinergic adverse effects. However, no documentation is given for attributing a number of these adverse effects to anticholinergic actions (e.g., encopresis). Using the more standard list of anticholinergic effects (dry eyes, dry mouth, constipation, urinary retention), overall, the rate of anticholinergic side effects was 4.8% in the tolterodine group and 3.5% in the placebo group.**
4) **Although the study report states that there is no difference in safety/tolerability regardless of method of administration, it is clear from Table 88 that subjects who used sprinkled beads had a much greater incidence of adverse effects. This may be related to the higher C_{max} of the sprinkled beads (or may be related to confounding factors, such as younger age, lower weight, or other characteristics found disproportionately in the group unable to swallow the capsule). This is not explored by the sponsor.**

14.8.4 Post Void Residual Urine Volume (PVR)

PVR was assessed by bladder ultrasonography at each visit and a value greater than 20% of theoretical bladder capacity was confirmed with a second scan. There were no instances of complete urinary retention. Over the course of treatment, the mean PVR increased by 0.68 ml in the tolterodine group and decreased by 2 ml in the placebo group. The incidence of PVR >= 20% of theoretical bladder capacity was 1.2% in the tolterodine group and 0.9% in the placebo group. Table 89 displays the data at each visit for the four subjects with elevated PVRs.

Table 89 Subjects with Elevated PVR (>= 20% of Theoretical Bladder Capacity)

Investigator/ Patient	Treatment	Age (y)/ Race/ Gender/ Weight (kg)	Visit	PVR (mL) First Scan	PVR (mL) Second Scan	Percent of Theoretical Bladder Capacity, First Scan	Percent of Theoretical Bladder Capacity, Second Scan	Date of Visit
56933/10074	Tolterodine PR 2 mg qd	10/W/F/27	Screening	79	5	21.94	1.39	2002-05-07
			Randomization	20		5.56		2002-05-16
			Treatment	73	76	20.28	21.11	2002-06-13
			End of treatment	62		17.22		2002-07-23
56840/10041	Placebo	5/W/F/27	Screening	54	34	25.71	16.19	2002-06-28
			Randomization	38		18.10		2002-07-17
			Treatment	39		16.25		2002-08-09
			End of treatment	79	56	32.92	23.33	2002-10-11
57181/10050	Tolterodine PR 2 mg qd	5/W/F/20	Screening	34		16.19		2002-05-31
			Randomization	9		4.29		2002-06-10
			Treatment	23		10.95		2002-07-02
			End of treatment	118	71	56.19	33.81	2002-09-04
57296/21060	Tolterodine PR 2 mg qd	5/W/F/20	Screening	0		0.00		2002-05-16
			Randomization	63	11	30.00	5.24	2002-05-27
			Treatment	112	102	53.33	48.57	2002-07-08
			End of treatment	112	102	53.33	48.57	2002-07-08

Source: Table 37, *5.3.5.1.4, p 107*

Medical Reviewer's comment:

Although the incidence of elevated PVR was not much greater in the tolterodine group than in the placebo group, the severity was. Two of the three tolterodine subjects had PVRs more than 50% of theoretical bladder capacity on at least one scan, and two tolterodine subjects were withdrawn from the study due to elevated PVR.

14.8.5 Vital Signs

Vital signs were obtained at baseline and at the end of treatment; however, the study report notes only that changes from baseline were small and not of clinical significance. Systolic and diastolic blood pressure and heart rate increased slightly from baseline in the tolterodine group; increases were smaller in the placebo group, and systolic blood pressure actually declined minimally in the placebo group.

14.9 Reviewer's assessment of efficacy and safety

The primary efficacy endpoint, change from baseline to week 12 in number of weekly incontinence episodes, was not statistically significantly different from placebo. Significant differences from baseline as compared to the placebo group were also not demonstrated in most of the secondary endpoints (change in number of incontinence episodes from baseline to week 4, number of micturitions/24 hours and frequency of nocturnal enuresis (the latter two variables at either four or at twelve weeks), proportion of subjects continent at the end of treatment, and in the quality of life instrument (PEMQoL) assessed at the end of treatment).

The mean volume of urine per micturition increased from baseline to both four and twelve weeks, with the difference in the tolterodine group being significantly greater than that seen in the placebo group. Categorization into one of five "improvement" categories at the end of treatment demonstrated a statistically significant advantage to the tolterodine group. The assessed parental satisfaction with treatment showed significantly greater satisfaction in the tolterodine group than the placebo group at the end of treatment on 3 of 10 questions (quality of life, symptoms and outcome).

Subgroup analyses were conducted to explore the effect of baseline weight on response to treatment. When subjects weighing over 35 kg were excluded from analysis, the treatment group did show significant improvement in number of weekly incontinence episodes.

Overall, there is no evidence of efficacy of tolterodine in significantly reducing the number of daily incontinence episodes among children aged 5 to 10 years with symptoms of urinary urgency and frequency suggestive of detrusor instability. The statistically significant increase in the volume of urine per micturition is small and of doubtful clinical significance.

There were no deaths and few serious adverse events in this study. The overall frequency of adverse events was similar between placebo and tolterodine treated subjects. The rate of anticholinergic side effects was slightly higher in the tolterodine group, but overall, was low in both groups. Laboratory and ECG data were not assessed in this study.

There were, however, signals regarding increased incidence of urinary tract infections and behavioral disorders in the tolterodine group, particularly worrisome since they were also noted in Study 020. The incidence of UTI was almost doubled (9.2 vs. 5.1%) in the tolterodine group, which may be related to the higher mean PVR noted in the treatment group. A number of psychiatric/behavioral complaints were reported in the tolterodine group, including four cases of abnormal behavior, one of which led to study withdrawal.

15 CLINICAL TRIAL 583E-URO-0084-021

15.1 Summary

Title: "Long-term Safety, Tolerability and Clinical Efficacy of Tolterodine Prolonged Release Capsules in Children 5-15 Years of Age" dated January 14, 2003.

Two amendments were made to Study 021, the first exclusively for the United States and one exclusively for Denmark. The first, dated February 19, 2001, included the following changes:

- Discontinuation from the study of any females who became pregnant
- Added urine pregnancy tests at the initial visit and every three months subsequently

Amendment #2, also dated February 19, 2001, included clerical changes to improve clarity and accuracy, exclusively for Denmark.

First patient entered: March 21, 2001

Last patient completed: July 31, 2002

15.2 Objectives

The primary objective of this study was:

- to study the long-term safety and tolerability of tolterodine PR over 12 months of treatment in children aged 5-15.

The secondary objectives were:

- to demonstrate long-term clinical efficacy of tolterodine PR in this population
- to perform other safety assessments

15.3 Overall Design

This multinational, multicenter, open label extension study was designed to evaluate the long-term safety and clinical efficacy of tolterodine PR daily over one year of treatment in 300 pediatric subjects aged 5 to 15 years, inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability. Subjects were eligible if they had completed either Study 018 or 020 previously. Efficacy data was collected based upon a micturition chart completed at months 6 and 12, as compared to baseline values.

The study was conducted at 45 sites in Europe (Austria, Belgium, Denmark, Germany, Norway, Russia, Slovenia, Sweden, The Netherlands and the U.K.), Asia (Hong Kong) and the U.S. The recruitment goal was 200-250 subjects, all to receive tolterodine, with the dose based on each subject's in the prior trial (all subjects from Study 020 received 2 mg, subjects from Study 018 received 2 or 4 mg). Withdrawn subjects who wished to re-enter the study were allowed to do so within 4 weeks after treatment cessation, as long as there were no safety concerns.

15.4 Study Procedures and Conduct

15.4.1 Schedule of Study Assessments

All subjects had previously completed a study using 2 or 4 mg daily of tolterodine extended release capsules. The extension study began at what is designated Visit 5, which was held where possible concurrently with the previous study's termination visit, or no more than four weeks later. The study drug was dispensed for the first three months at this visit. Return visits occurred at three-month intervals, at which time medication for the next three months' treatment was given out. A micturition diary was given to subjects at Visits 6 and 8 and collected at the subsequent visits. Table 90 outlines the procedures completed at each study visit.

Table 90 Schedule of Study Assessments

Part of study period	Inclusion	Treatment period				
Visit number*	5	Telephone contact	6	7	8	9
Month in study	0	1 - 2 weeks after Visit 5	3	6	9	12
Visit window (± days)			± 7	± 7	± 7	± 7
Written informed consent	X					
Inclusion/exclusion criteria	X					
Adverse events	X	X	X	X	X	X†
Concomitant medication	X	X	X	X	X	X
Urine pregnancy test**	X		X	X	X	X
MSU for dipstick, culture/microscopy				X		X
PVR			X			X
Compliance to treatment			X	X	X	X
Drug dispensing	X		X	X	X	
Drug accountability			X	X	X	X
Dispensing of micturition chart			X		X	
Collection of micturition chart				X		X
Blood sample (lab analyses)						X
VASC (020)						X
Benefit of treatment						X

* Visits 1 - 2 (018) and 1 - 4 (020) are in the previous study.
** Required only for female patients from Study 018.
† All drug-related or serious adverse events were followed until they resolved or were declared "stable" or "chronic."
MSU = midstream specimen of urine; PVR = post-void residual urine volume; VASC = Visual Analogue Scale for Children.

Source: Table 1, *5.3.5.1.3, p 21*

15.5 Study Drug

15.5.1 Dose Selection

The drug studied was tolterodine prolonged release (PR) 2 or 4 mg capsules, taken once daily. This dose was chosen based on the dose each subject received in the previous study. The drug was to be taken daily in the morning and swallowed whole with water.

Medical Reviewer's comments:

1) **Although it is not clearly stated, it appears that subjects who received placebo in Study 020 were started on 2 mg of tolterodine in Study 021.**
2) **It appears that subjects were instructed to swallow the capsules whole. The experience of subjects who were unable to swallow capsules and therefore used the sprinkled beads method of administration in Study 020 is not described.**

15.5.2 Choice of Comparator

This was an open-label study; no comparator or placebo was used.

15.5.3 Assignment to Study Drug

There was no randomization to or blinding of treatment assignment.

15.6 Patient Population

Study 021 included subjects who had previously participated in Studies 020 or 018; thus, it was a heterogeneous population. Table 91 displays the differences in the two populations. Table 92 identifies the subjects comprising the ITT, safety and completer populations.

Table 91 Patient Differences by Previous Study

Design Feature	Study 020	Study 018
Age	5 – 10 years	11 – 15 years
Inclusion criteria	≥ one incontinence or dampness episode/day for ≥ 5/7 days, and > two micturitions/24 hours	Urinary urgency and ≥ eight micturitions/24 hours, AND/OR ≥ one incontinence episode/week
Treatment	Randomized and double-blind, two thirds of patients treated with tolterodine PR 2 mg qd, and one third with placebo for 12 weeks	Open-label pharmacokinetic study; first 10 patients treated with tolterodine PR 2 mg qd, and next 21 with tolterodine PR 4 mg qd for 7 (6 - 10) days
Eligible for enrollment in 021	302 (of 342 randomized)	31 (of 31 enrolled)
Micturition chart data	Incontinence episodes during waking hours only. Episodes of "gross" incontinence separated from "dampness," except in UK.	Incontinence episodes during a 24-hour period, not just waking hours. No distinction made between "gross" incontinence and "dampness."

Source: Table 2, *5.3.5.1.3, p 25*

Table 92 Overview of Analysis Populations

Population	Treatment Group					
	Tolterodine PR 2 mg qd (020)		Tolterodine PR 2 mg qd (018)		Tolterodine PR 2 mg qd (018)	
	n	%	n	%	n	%
Enrolled	273	100	7	100	20	100
Enrolled and not treated	2	0.7	0	0	0	0
Safety/ITT population*	271	99.3	7	100	20	100
Withdrawn from study	117	43.2	4	57.1	7	35.0
Completer population**	154	56.8	3	42.9	13	65.0

* All included patients who had taken at least one dose of study medication.
** All included patients who completed the study.
Source: Table 7, *5.3.5.1.3, p 47*

15.6.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Subject appropriately included in and completed Study 018 or 020

2. Participants/parents(s)/legal guardians(s) have provided written informed consent to participate in the study

Exclusion Criteria

1. Any condition which, in the investigator's opinion, made the subject unsuitable for inclusion
2. History of urinary retention, or PVR >= 20% of theoretical bladder capacity in the previous study
3. Severe constipation requiring rectal treatment and/or not responding to oral treatment
4. Post-menarchal females (Study 020) or not using adequate contraception (Study 018)
5. Significant indication of hepatic or renal compromise, or evidence of hematuria at the end of the prior study
6. Participants taking any medications know to affect the lower urinary tract (except desmopressin for nocturnal enuresis in Study 020 only) or anticholinergic drugs or on an unstable dose of any drug with anticholinergic side effects
7. Any contraindications to or intolerance of anticholinergic therapy
8. Participants with known allergy to tolterodine or its excipients
9. Participants who are currently taking antibiotics which interact with CYP3A4 metabolism such as antifungals or aminoglycosides

15.6.2 Demographics and Baseline Disease Characteristics

Forty-five European, Asian and American sites enrolled a total of 300 subjects. Belgium accounted for almost one-fourth of the subjects. Table 93 provides the breakdown by country for the 300 subjects. The study comprises 273 subjects of the original 342 from Study 020 and 27 from the original 29 in Study 018 (seven of nine who received the 2 mg dose and all twenty who received the 4 mg dose). The Intention to Treat (ITT)/safety population excludes two subjects from Study 020 who never took any study drug in Study 021. The Completer population excludes the 128 subjects who withdrew from the study (117 from Study 020 and 11 from Study 018).

Table 93 Subject Enrollment by Country

Country	Treatment in Study 021			
	Tolterodine PR 2 mg qd (020)	Tolterodine PR 2 mg qd (018)	Tolterodine PR 4 mg qd (018)	Total per country
Austria	18			18
Belgium	67			67
Denmark	26			26
Germany	13			13
Hong Kong	11			11
Netherlands	21			21
Norway	34			34
Russia	23			23
Slovenia	8			8
Sweden	13			13
United Kingdom	39			39
USA		7	20	27
Total per Treatment	273	7	20	300

Source: Table 4, *5.3.5.1.4, p 42*

Baseline and demographic characteristics for the ITT population are summarized in Table 94, compiled by the reviewer, as the study reports data separately for Study 020 and Study 018 subjects. These characteristics were recorded at baseline for the original trial; data for the subjects originating in Study 020 are in Table 57 and Table 58. The trial enrolled a slight plurality of males. Over 90% were Caucasian, with almost all the remaining subjects being Asian/Pacific Islander. Approximately 90% were extensive metabolizers.

Table 94 Demographic Characteristics of ITT Population

Characteristic	Safety Population N = 298		Completer Population N = 170	
	N	%	N	%
Gender - Male	165	55.4	96	56.5
Female	133	44.6	74	43.5
Age Group				
5-6 years	67	22.5	38	22.4
7-8 years	121	40.6	69	40.6
9-11 years *	83	27.9	47	27.6
11-12 years *	15	5.0	9	5.3
13-14 years	12	4.0	7	4.1
Race - White	274	91.9	157	92.4
Asian/Pacific Island	17	5.7	10	5.9
Black	4	1.3	2	1.2
Mixed	3	1.0	1	0.6
Genotype – EM	267	89.6	153	90.0
PM	14	4.7	9	5.3
Missing	17	5.7	8	4.7

*These age groups overlap due to different age inclusions in Studies 020 and 018
Source: Tables 8 & 30, *5.3.5.1.4, pp 48, 104*

15.6.3 Withdrawals, compliance, and protocol violations

One hundred twenty-eight subjects discontinued the trial early, representing 43% of subjects enrolling from Study 020 and 57% of those originally in Study 018 (Table 95). The most common reason for withdrawal was lack of efficacy, accounting for 37% of all withdrawals. Twenty-six percent of withdrawals occurred due to improvement. Eight subjects (6% of withdrawals) withdrew due to adverse events (see Section 15.8.3).

Subjects were allowed to reenter the study within four weeks of a withdrawal, and were not counted among the withdrawals in this case. Seven subjects fell into this category including two who originally withdrew due to an adverse event (eye edema and planned surgery). Six of these subjects did complete the trial; one withdrew a second time (both times due to lack of efficacy).

Medical Reviewer's comment:

Although the protocol specifies that subjects must re-enter within four weeks of withdrawal, four of the seven re-entries exceeded this limit. The range of the interval from withdrawal to re-entry was 10-78 days. The two subjects who withdrew due to adverse events both exceeded the 28 day interval between withdrawal and re-entry, and therefore should be counted among subjects who withdrew due to adverse events.

Table 95 Reasons for Withdrawal by Study of Origin

Reason for Withdrawal*	Treatment in Study 021						Total	
	Tolterodine PR 2 mg qd (020)		Tolterodine PR 2 mg qd (018)		Tolterodine PR 4 mg qd (018)			
	N = 271		N = 7		N = 20		N = 298	
	n	%	n	%	n	%	n	%
Adverse event	8	3.0					8	2.7
Protocol violation	2	0.7			1	5.0	3	1.0
Consent withdrawn	14	5.2	3	42.9	6	30.0	23	7.7
Lost to follow-up	13	4.8	1	14.3			14	4.7
Lack of efficacy	47	17.3					47	15.8
Improvement	33	12.2					33	11.1
Total	117	43.2	4	57.1	7	35.0	128	43.0

* The last withdrawal reason is used for reentered patients.
Source: Table 5, *5.3.5.1.4, p 44*

Compliance was assessed by comparison of expected number of capsules taken to amount of unused study medication returned at Visits 3 and 4. Compliance was defined as actual use >=75% of expected use. The investigator also assessed compliance at each visit by discussion with the patient. Compliance across the study averaged 84%, however, it was greater in the subjects from Study 020 (87%) than those from 018 (59%).

Medical Reviewer's comment:

The protocol specifies two methods of determining compliance: drug counts and investigator assessment. The results state that compliance was determined based on drug counts, but notes that the investigator's assessment was not always in accord. At Visit 9, investigators assessed only 66% of the subjects to be >= 75% compliant.

Protocol violation criteria were defined a priori and subjects categorized as violators prior to closure of the database. Major protocol violations occurred in 93 subjects (31%). Specific violations are noted in Table 96. The vast majority concern unusable micturition chart data.

Table 96 Major Protocol Violations by Group

Protocol Violation**	Number (%)* of patients			
	Tolterodine PR 2 mg qd (020) N = 271	Tolterodine PR 2 mg qd (018) N = 7	Tolterodine PR 4 mg qd (018) N = 20	Total N = 298
Violation of eligibility	1 (0.4)			1 (0.3)
Time interval between studies > 60 days	4 (1.5)			4 (1.3)
Reentered after > 10 weeks	1 (0.4)			1 (0.3)
Missing/invalid micturition charts at both Visits 7 & 9	51 (18.8)	4 (57.1)	6 (30.0)	61 (20.5)
Compliance < 75%	18 (6.6)	1 (14.3)	5 (25.0)	24 (8.1)
Prohibited medication	2 (0.7)			2 (0.7)
PVR not done	17 (6.3)		1 (5.0)	18 (6.0)
Total number major violations	94	5	12	111
Total number (%) patients with major violation(s)**	77 (28.4)	4 (57.1)	12 (60.0)	93 (31.2)

* Percentage of the total number of patients in each treatment group.
** Patients may have more than one major violation.
Source: Table 6, *5.3.5.1.4, p 45*

Medical reviewer comments:

1) **The absence or unreliability of 20% of the data used for several of the major efficacy endpoints is a significant review issue.**
2) **The report is contradictory on the inclusion of subjects with < 75% compliance. It notes that these subjects were not excluded from the completer population; however, their data were excluded from the micturition chart analysis.**

15.7 Efficacy

15.7.1 Key Efficacy Assessments

The clinical efficacy variables were based on the micturition charts, and on the Visual Analog Scale for Children (VASC) for subjects 9 years or older. The VASC is a validated questionnaire with six subscales used to measure the subject's well-being (alertness, self-esteem, mood, inhibition, stability and litheness). This scale was administered only to those subjects from Study 020 aged 9 and greater.

Parental or subject assessment as to the benefit from treatment was also assessed, at Visit 9, and rated as "no," "little" or "much" improvement. The micturition charts were completed over the 7 days preceding Visits 7 and 9. Variables from the charts were:

- Change from baseline to month 12 in weekly number of incontinence episodes (during waking hours for subjects from Study 020)
- Change from baseline to month 12 in number of micturitions over 24 hours
- Change from baseline to month 12 in urinary volume voided (using a measuring vessel provided to the subject) (subjects from Study 020)
- Whether the previous night was wet or dry (subjects from Study 020)

Subjects from Study 020 were instructed to record all problematic episodes as "major" incontinence; minor, insignificant leakage was recorded as "dampness." (This distinction was not made in the UK,

or in Study 018.) Data obtained during a period when the investigator suspected a UTI was excluded if the UTI was confirmed by culture or if culture was unavailable.

Additional, exploratory, analyses pre-specified in the protocol included subgroup tabulations by age, gender and body weight for number of weekly incontinence episodes.

Medical reviewer comments:

1) **Although generally the micturition chart data were collected over 7 days, the volume/void was measured on only 2 of the 7 diary days. It is not specified which two days were chosen, whether they were consecutive and whether the choice of days was made by the subject/parent, by the investigator, or pre-specified in the protocol.**
2) **Data collected during a culture-positive UTI occurring when the investigator had not suspected a UTI was included (4 cases). This introduces a possible bias, as variables in the micturition chart may influence the investigator's suspicion of UTI.**
3) **The use of whether the prior night was dry was not specified as an efficacy endpoint in the protocol.**
4) **As noted in the review of Study 020, it appears that the VASC was developed for and validated on children with short stature, not incontinence.**

15.7.2 Pharmacokinetic Assessments

No pharmacokinetic assessments were conducted in Study 021.

15.7.3 Primary Efficacy Endpoint Analysis

All efficacy measures were considered secondary endpoints in this study, since its primary objective was to study long-term safety. Efficacy data was analyzed separately for subjects originating in Study 020 and in Study 018, and the results presented here will focus on subjects from Study 020, who were all on the same dose of tolterodine as used in the two previous controlled trials, and who constituted over 90% of Study 021 participants. Subgroup analysis was also conducted dividing subjects into those the baseline urinary < or >= 6 micturitions/24 hours, and on age, gender and weight groups.

The main efficacy endpoint analyzed was change from baseline to month 12 in number of weekly incontinence episodes during waking hours. The analysis was conducted on the ITT/safety and completer populations. Only descriptive statistics are reported; significance testing was not done. Data on reduction in the number of weekly incontinence episodes are shown in Table 97. In the ITT population, there was a reduction of 8.6 weekly episodes at month 6 of treatment and of 9.1 episodes at month 12, as compared to a baseline frequency of 14.3 episodes per week.

Table 97 Change in Weekly Incontinence Episodes

Number of incontinence episodes/week		Safety Population N = 271	Completer Population N = 154
Missing (baseline and/or both Visits 7 and 9)		54	3
Baseline	Mean (SD)	14.3 (8.6)	14.7 (8.8)
	Median (min – max)	12.6	13.0
	n	217	151
Visit 7/Month 6	Mean (SD)	5.7 (8.2)	5.8 (8.2)
	Median (min – max)	3.0	3.3
	n	217	148
Visit 9/Month 12 or withdrawal	Mean (SD)	5.2 (9.6)	4.8 (10.3)
	Median (min – max)	3.0	3.0
	n	217	147
Change from baseline to Month 6	Mean (SD)	-8.6 (8.7)	-9.0 (9.4)
	Median (min – max)	-7.7	-8.2
	95% CI	(-9.8, -7.5)	(-10.5, -7.5)
	n	217	148
Change from baseline to Month 12	Mean (SD)	-9.1 (9.6)	-9.7 (10.4)
	Median (min – max)	-8.0	-9.0
	95% CI	(-10.4, -7.8)	(-11.4, -8.0)
	n	217	147

The number of incontinence episodes/week was set to a maximum of 112.
For the safety population: carry forward/backward between Visits 7 and 9.
Source: Table 11, *5.3.5.1.4, p 53*

Sub-grouped by baseline urinary frequency, both groups showed improvement of similar proportion: those with >= 6 micturitions/day dropped from 15.4 weekly incontinence episodes at baseline to 6.0 at month 12 (a decrease of 9.4/week) while those with < 6 micturitions/day decreased from a baseline frequency of 13.1 episodes per week to 4.3 at month 12 (a change of -8.8 episodes/week). Results were similar, although of slightly lesser magnitude at month 6. Restratifying into >7 and <= 7 micturitions/day, results were similar, although more striking in the subgroup with greater baseline frequency (a decrease at month 12 of 10.9 episodes/week vs. 8.3 in the less frequent group). The populations were further enriched by sub-grouping according to >= 6 micturitions/day AND >=10 incontinence episodes/week, and results again favored the more severe group.

Finally, subgroup analyses were also performed to look at the effect of age, gender and body weight on number of weekly incontinence episodes. There were improvements favoring children aged 7-8 years, females and those <20 kg. However, it is noted that those subgroups with greatest improvement also had the highest frequency of baseline incontinence. Table 98 presents the results of these subgroup analyses on the change in weekly frequency of incontinence.

Table 98 Change from Baseline in Weekly Incontinence by Analysis Subgroup

Subgroup	Baseline	Month 6	Month 12	Change at Month 6	Change at Month 12
Age group					
Age 5-6 N=55	13.5	5.8	4.3	-7.7	-9.2
Age 7-8 N=94	15.6	5.6	4.9	-10.0	-10.6
Age 9-11 N=68	13.3	5.7	6.3	-7.6	-6.9
Gender					
Male N=117	13.9	6.1	5.8	-7.8	-8.1
Female N=100	14.8	5.2	4.6	-9.6	-10.2
Weight Gp					
< 20 kg N=31	14.8	4.6	3.6	-10.3	-11.2
20 to <30 kg N=127	14.2	6.6	5.9	-7.6	-8.3
>= 30 kg N=59	14.3	4.4	4.6	-9.9	-9.7

Source: Tables 40-42 , *5.3.5.1.4, pp 111-112*

Medical Reviewer Comment:

In the absence of a placebo control, it is not possible to determine if the efficacy results represent a true treatment effect, the maturational effect of time, or regression toward the mean amplified in those groups with more severe baseline values.

15.7.4 Secondary Efficacy Endpoint Analysis

Additional secondary endpoints were mean change from baseline to month 12 in number of micturitions/24 hours, urinary volume/void, number of dry nights/week, as well as achievement of continence, well-being as assessed by the VASC and parental assessment of treatment benefit. Number of micturitions per 24 hours was not reported for the entire ITT group; rather, two subgroup analyses based on urinary frequency at baseline (cutting baseline urinary frequency at >= 6 micturitions/24 hours and at >7 micturitions/24 hours) were conducted. Subjects with baseline frequency of >= 6 micturitions/day had a decrease of 1.7 micturitions daily at both the 6 and 12 month assessments, while those with fewer than six daily micturitions at baseline had a minimally increased urinary frequency (0.1 micturitions at month 6 and 0.2 at month 12). Results were similar with the cut made at >7 micturitions/day at baseline.

Similarly, only subgroup analyses, using the same cut-points, are presented for the variable urinary volume/void. Increases were seen in both the "normal frequency" subgroup, and the "pathological frequency" subgroup at both cut-points.

The number of dry nights per week increased from a baseline average of 2.6 to 3.9 by Month 6 and to 4.3 by Month 12. The proportion fully continent during daytime hours was 25.5% by Month 6 and 28.4% by Month 12, although almost 20% of the subjects had no data on this variable. Over half the population remained incontinent at both time points. Evaluation of five degrees of improvement (worse, none, minimal, moderate and 100% continent) showed that, of those with data on this variable, almost 90% had experienced minimal to 100% improvement at each time point.

The VASC scale was administered only to subjects aged nine or older from Study 020, or approximately 18% of the ITT population. Confidence intervals around the change from baseline to Month 12 included 0 on each of the six subscales, indicating no significant change.

Parental perception of treatment benefit is presented in Table 99. Although there were considerable missing data, almost half of parents considered that their child had received much benefit from treatment

Table 99 Parent-Perceived Treatment Benefit by Group

Parent/guardian assessment of treatment benefit	Safety Population N = 271		Completer Population N = 154	
	n	%	n	%
No Benefit	36	13.3	15	9.7
Little Benefit	54	19.9	41	26.6
Much Benefit	130	48.0	98	63.6
Missing	51	18.8		

Source: T 54, *5.3.5.1.3, p 121*

Medical Reviewer's comment:

Data on change in number of micturitions/24 hours and volume/void should be presented for the entire ITT population. Sub-group analyses are exploratory and should not be the only analyses reported.

15.8 Safety

15.8.1 Safety Measurements

All participants who received at least one dose of study medication were to be included in the summaries and listings of safety data. Adverse events were coded according to the Medical Dictionary for Regulatory Action (MedDRA) and were summarized by organ system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events (by participant, parent, or guardian)
- Pregnancy outcome in any cases of exposure in utero
- Change in laboratory assessment (hematology and serum chemistries) from baseline to Visit 9
- Urinalysis, with microscopy and culture if dipstick positive, done at Visits 7 and 9
- Pregnancy tests on all female subjects of child-bearing potential at 3 month intervals throughout the study
- Post void residual urine volume (PVR), measured by bladder ultrasonography at visits 6 and 9. A positive scan was defined as >=20% of the theoretical bladder capacity, computed by [30 + (30*age)]. (This is the same formula used in Study 020.)

15.8.2 Extent of exposure

Time in study is displayed in Table 100. It should be noted that duration includes the term of the original study as well as time in Study 021; thus, subjects from Study 018, which lasted only 7 days, have shorter overall duration even if their time in Study 021 equaled that of subjects from Study 020.

Table 100 Treatment Duration by Study of Origin

Duration of treatment (months)	Tolterodine PR 2 mg qd (020) N = 271		Tolterodine PR 2 mg qd (018) N = 7		Tolterodine PR 4 mg qd (018) N = 20	
	n	%	n	%	n	%
0 – < 1	262	96.7	7	100.0	17	85.0
1 – < 2	259	95.6	6	85.7	16	80.0
2 – < 3	257	94.8	6	85.7	14	70.0
3 – < 4	254	93.7	6	85.7	14	70.0
4 – < 5	240	88.6	3	42.9	13	65.0
5 – < 6	236	87.1	3	42.9	13	65.0
6 – < 7	221	81.5	3	42.9	13	65.0
7 – < 8	209	77.1	3	42.9	13	65.0
8 – < 9	205	75.6	3	42.9	13	65.0
9 – < 10	190	70.1	3	42.9	13	65.0
10 – < 11	184	67.9	3	42.9	13	65.0
11 – < 12	176	64.9	3	42.9	13	65.0
12 – < 13	143	52.8	3	42.9	11	55.0
13 – < 14	112	41.3				
14 – < 15	100	36.9				
≥ 15	29	10.7				
Missing	9	3.3			3	15.0

Source: Table 10, *5.3.5.1.3, p 50*

Medical Reviewer's comment:

The expected duration of overall participation by subjects originating in Study 020 would be 15 months (three in Study 020 and 12 in Study 021). Eight-nine percent of subjects ended participation before this. Even allowing for subjects who had their final Study 021 visit one week short of 12 months, as allowed in the study protocol, over 63% of subjects from Study 020 failed to complete the full length of Study 021.

15.8.3 Serious adverse events

Deaths: there were no deaths.

Premature termination due to safety reasons: Eight subjects, all originating from Study 020, terminated prematurely from the study because of eleven adverse events. They are listed in Table 101. One event was severe (aggravated aggression), and all but one moderate event (aggravated incontinence) were judged to be treatment related. The most common adverse events leading to withdrawal were behavioral disorders (3: aggravated aggression, increased activity and attention disturbance) and difficulty in micturition (2). The adverse events tended to occur in the first half of the treatment course, with five of eight occurring in the 3-6 month interval.

Medical Reviewer's comment:

Subjects # 307 and 315 also should have been counted as withdrawals due to adverse events, as they re-entered the study beyond the pre-specified time limit. Subject 307 withdrew due to eye edema and was off medication for 37 days prior to reentry. Subject 315 had a planned surgery for implantation of a new lens (lost to trauma prior to study enrollment) and was off medication for 32 days. Both of these adverse events were judged not to be related to medication.

Table 101 Withdrawals due to Adverse Events

Patient number /age/gender /race/weight	Preferred term (MedDRA)	Day of onset	Duration (days)	Maximum intensity	Related to study medication?	Outcome	Outcome at follow-up	Is event chronic or stable?
211/6/M/W/25	Aggression aggravated	81	39	Severe	Yes	Recovered with sequelae		
240/9/M/W/31	Nausea	259	8	Mild	Yes	Recovered		
	Headache NOS	259	8	Mild	Yes	Recovered		
246/10/M/W/40	Difficulty in micturition	95		Mild	Yes	Unknown		
249/6/M/W/20	Increased activity	11	108	Moderate	Yes	Recovered with sequelae		
267/7/F/A/19	Dry skin	17	138	Mild	Yes	Recovered		
268/8/M/A/22	Disturbance in attention NEC	-136		Mild	Yes	Unknown	Recovered	
477/7/M/W/25	Constipation	14	5	Mild	Yes	Recovered		
	Abdominal pain NOS	14	5	Mild	Yes	Recovered		
503/7/F/W/19	Difficulty in micturition	104		Mild	Yes	Not recovered	Not recovered	Yes
	Urinary incontinence aggravated	106		Moderate	No*	Not recovered		

The age was calculated at Visit 5.
Two reentered patients, withdrawn due to AEs, are not included in this table as they later completed the study.

Source: Table 24, *5.3.5.1.4, p 78*

Serious adverse events: Eight subjects, all originating from Study 020, experienced serious adverse events (SAEs). They are listed in Table 102. None of the SAEs resulted in withdrawal and none were considered treatment related. SAEs occurred in three females and five males and tended to occur in younger and smaller children (seven were aged eight or under, weights ranged from 19-34 kg).

Details of the individual cases are:

- #119 – patient with a previous history of UTI experienced pyelonephritis in month 7 of the study, recovered and was maintained on antibiotic prophylaxis
- #173 – fractured left arm
- #237 – hospitalized with vomiting and dehydration approximately five months into the trial
- #259 – fractured left femur
- #315 – subject with previous history of eye trauma (loss of lens), hospitalized for planned implantation of new lens
- #335 – hospitalized for a lumbar puncture for unknown indication, treated for vomiting the next day
- #336 – experienced testicular torsion requiring surgery
- #485 – hospitalized with pneumonia for treatment with IV antibiotics

Table 102 Serious Adverse Events

Treatment	Patient number/ age/gender/race/weight	Preferred Term (MedDRA)	Withdrawn due to AE (Yes/No)	Outcome	Outcome at follow-up*	Related to treatment?
Tolterodine PR 2 mg qd (Study 020)						
	119 / 6 / F / W / 19	Pyrexia	No	Recovered		No
		Pyelonephritis NOS	No	Recovered		No
	173 / 7 / M / W / 19	Fracture NOS	No	Not Recovered	Recovered	No
	237 / 6 / M / W / 22	Vomiting NOS	No	Recovered		No
		Dehydration	No	Recovered		No
	259 / 8 / M / A / 19	Femur fracture NOS	No	Recovered		No
	315 / 8 / M / W / 34	Lens implant	No	Recovered		No
	335 / 8 / F / W / 28	Lumbar puncture	No	Recovered		No
	336 / 6 / M / W / 19	Testicular torsion	No	Recovered		No
	485 / 9 / F / W / 31	Pneumonia NOS	No	Recovered		No

The age was calculated at Visit 5.
* Outcome at follow-up at the end of study treatment
** Patient 315 was withdrawn due to surgery but reentered the study and completed 12 months of treatment See Section 7.1.1.

Source: Table 23, *5.3.5.1.4, p 76*

15.8.4 Frequent adverse events

As subjects entered Study 021 directly from a previous study, it is notable that 10-20% of subjects, depending on the study of origin, entered this extension study with ongoing adverse events that begin in the previous study. New onset adverse events occurred in 156 subjects, or 52% of all subjects, for a total of 351 events. The *most* frequent adverse events were UTI, abdominal pain, cough, headache, nasopharyngitis, constipation, and vomiting.

Regarding anticholinergic side effects, constipation occurred in 3.7 % and abdominal pain in 7.4%. Dry mouth was reported in 1.1% of subjects, dry eyes were not reported. There were no reported cases of frank urinary retention, but difficulty in micturition occurred in 1.8% of subjects.

Table 103 presents the adverse events occurring in ≥1% of subjects. Adverse event data broken down by age, gender and weight groups are shown in Table 104. The overall prevalence of adverse events decreases with age, with subjects aged 5-6 having the greatest frequency of adverse events, both ongoing, and of new onset during Study 021. The same pattern was seen when subdivided by weight, particularly for new-onset adverse events. There was a slightly higher frequency among females.

Table 103 Adverse Events Reported by ≥1% of Subjects

MedDRA System Organ Class and Preferred Term		Tolterodine PR 2 mg qd (020) N = 271				Tolterodine PR 2 mg qd (018) N = 7		Tolterodine PR 4 mg qd (018) N = 20			
		Ongoing at entry		Onset during study		Onset during study		Ongoing at entry		Onset during study	
		n	%	n	%	n	%	n	%)	n	%
Ear and labyrinth disorders	Earache			3	1.1						
Gastrointestinal disorders	Abdominal pain NOS	2	0.7	10	3.7						
	Abdominal pain upper			10	3.7						
	Constipation	2	0.7	10	3.7						
	Diarrhea NOS	1	0.4	8	3.0						
	Dry mouth	2	0.7	3	1.1						
	Fecal incontinence	1	0.4	5	1.8						
	Nausea	1	0.4	3	1.1						
	Sore throat NOS			3	1.1						
	Vomiting NOS			9	3.3					1	5.0
General disorders and administration site conditions	Fatigue	1	0.4	4	1.5						
	Pyrexia			7	2.6						
Infections and infestations	Ear infection NOS			3	1.1						
	Gastroenteritis NOS			4	1.5						
	Impetigo NOS			3	1.1						
	Infection NOS			4	1.5						
	Influenza			12	4.4						
	Nasopharyngitis			15	5.5	2	28.6				
	Sinusitis NOS			3	1.1			1	5.0		
	Tonsillitis NOS			3	1.1						
	Upper respiratory tract infection NOS	1	0.4	7	2.6						
	Urinary tract infection NOS	3	1.1	19	7.0	1	14.3	1	5.0	2	10.0
	Viral infection NOS			3	1.1						
Injury and poisoning	Accident NOS				3	1.1				1	5.0
Nervous system disorders	Headache NOS	3	1.1	16	5.9						
Psychiatric disorders	Aggression				3	1.1					
Renal and urinary disorders	Difficulty in micturition				5	1.8					
	Urinary incontinence aggravated				3	1.1					
Respiratory, thoracic, and mediastinal disorders	Cough	2	0.7	19	7.0						
	Epistaxis	1	0.4	4	1.5	1	14.3				
	Rhinitis NOS			5	1.8						
	Rhinitis allergic NOS			3	1.1						
	Rhinorrhea			3	1.1						
Skin and subcutaneous tissue disorders	Dermatitis NOS	1	0.4	6	2.2						
	Dry skin			3	1.1						

Source: Table 18, *5.3.5.1.3, pp 67-69*

Table 104 Adverse Event Rates by Age, Gender and Weight Groups

Patients divided by age group	5 – 6 years N = 67		7 – 8 years N = 121		9 – 11 years N = 83		5 – 6 years N = 67		7 – 8 years N = 121		9 – 11 years N = 83	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients with at least one adverse event	10	14.9	12	9.9	7	8.4	46	68.7	64	52.9	36	43.4
Total number of events	13		20		7		113		138		84	

Patients divided by gender	Male N = 155		Female N = 116		Male N = 155		Female N = 116	
	n	%	n	%	n	%	n	%
Total number of patients with at least one adverse event	14	9.0	15	12.9	82	52.9	64	55.2
Total number of events	16		24		164		171	

Patients divided by weight group	< 20 kg N = 35		≥20–<30kg N = 161		≥ 30 kg N = 75		< 20 kg N = 35		≥20–<30kg N = 161		≥ 30 kg N = 75	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients with at least one adverse event	8	22.9	13	8.1	8	10.7	24	68.6	88	54.7	34	45.3
Total number of events	8		22		10		70		186		79	

- Patients with more than one adverse event were counted only once in each category (ongoing at entry or onset during study).
- Total number of events by MedDRA *preferred term*: for each patient any event was counted only once (in each category) regardless of the number of times it was reported during the study.

Source: Table 71, *5.3.5.1.3, p 146*

Medical Reviewer's comments:

1) **Viewed by individual common adverse events, there are potentially concerning signals of abnormal behavior in 2% (six cases occurred, including self-mutilation, abnormal behavior NOS, aggression and aggravated aggression) and a single case of "intermittent cerebral claudication."**
2) **As this trial did not use weight-based dosing, the decreased incidence of adverse events with increasing body weight suggests that adverse events are associated with drug exposure. The very similar new-onset adverse event rates by age and by weight groups suggests a strong correlation between these two baseline variables.**
3) **UTIs occurred exclusively in females.**
4) **Table 94 includes only those subjects originating in Study 020. Equivalently subdivided data from Study 021 subjects are not provided.**

15.8.5 Laboratory Values and Urinalysis

The serum chemistry, hematology, and urinalysis test results were reviewed. Shifts from baseline in laboratory parameters are presented in Table 105. Single cases each of elevated ALT and elevated AST were reported among the laboratory shifts.

Table 105 Shifts from Baseline in Laboratory Safety Variables

Laboratory Variable			Tolterodine PR 2 mg qd (020) N = 271			Tolterodine PR 2 mg qd (018) N = 7			Tolterodine PR 4 mg qd (018) N = 20		
			Up	Down	Missing	Up	Down	Missing	Up	Down	Missing
Hematology	Erythrocytes (RBC)	x 10^{12}/L	2		135			4			6
	Hemoglobin	g/L		3	135			4			6
	Leukocytes (WBC)	x 10^{9}/L		8	144	2		4	1		6
	Platelet Count	x 10^{9}/L	1		137			4			6
Chemistry	Alkaline Phosphatase (ALP)	U/L	1		127		1	4		1	6
	Alanine Aminotransferase (ALT)	U/L	1		127			4			6
	Aspartate Aminotransferase (AST)	U/L		6	127	1		4			6
	Bilirubin	umol/L	1	2	128			4			6
	Creatinine	umol/L	4		127			4		2	6
	Potassium (K)	mmol/L			127			4			6
	Sodium (NA)	mmol/L			127			4		1	6
	Thyroid-Stimulating Hormone (TSH)	mU/L	1		139			4			6

Source: Table 74, *5.3.5.1.3, p 150*

Medical Reviewer's comments:

1) **Laboratory safety data is missing in up to 52% of the variables.**
2) **The data on shifts in laboratory data include only those cases in which baseline values were within normal range. Overall, there was one case of ALT elevation, from 28 at baseline to 57 at month 12, and two cases of AST elevation, one from a baseline of 25 to 56, and one from an elevated baseline value of 73 to 78.**
3) **No summaries of urinalysis data are provided.**

15.8.6 Pregnancy Outcome

Urine pregnancy tests were obtained on all postmenarchal female subjects from Study 018 at baseline and subsequently, at three month intervals. There were no positive pregnancy tests.

15.8.7 Post Void Residual Urine Volume (PVR)

PVR was assessed at Months 3 and 12. Three subjects entered Study 021 with elevated PVRs diagnosed at the end of the prior study, and were considered to be minor protocol violators. Six subjects developed PVR >= 20% of theoretical bladder capacity during the study (Table 106). One additional subject experienced difficulty in micturition without an elevated PVR. Overall, PVR increased very little over the course of the study (mean increase of 3 ml at 12 months). The maximal PVR reported was 314 ml.

Table 106 Shifts in PVR from Baseline Value

PVR ** (% of theoretical bladder capacity)		Tolterodine PR 2 mg qd (020) N = 271				Tolterodine PR 2 mg qd (018) N = 7		Tolterodine PR 4 mg qd (018) N = 20	
		Baseline PVR < 20% N = 268		Baseline PVR ≥ 20% N = 3		Baseline PVR < 20% N = 7		Baseline PVR < 20% N = 20	
		n	%	n	%	n	%	n	%
Visit 6/Month 3	< 20%	232	85.6	3	1.1	3	42.9	13	65.0
	≥ 20%	1	0.4						
	Missing	35	12.9			4	57.1	7	35.0
Visit 9/Month 12 or withdrawal	< 20%	189	69.7	1	0.4	4	57.1	14	70.0
	≥ 20%	5	1.8	1	0.4				
	Missing	74	27.3	1	0.4	3	42.9	6	30.0

Source: Table 25, *5.3.5.1.3, p 80*

15.8.8 ECGs

ECGs were not obtained in this study.

15.8.9 Vital Signs

Vital signs were not obtained in this study.

15.9 Reviewer's assessment of efficacy and safety

Efficacy endpoints were not considered primary in this study, as the primary objective was to study the long-term safety of tolterodine, and the study was uncontrolled. Thus, no statistical assessment of efficacy can be made. There was a reduction from baseline to month 6 in the main efficacy outcome variable, number of weekly daytime incontinence episodes, which appeared to be maintained at 12 months of treatment. Data for several of the other efficacy endpoints are presented only for subgroups based on urinary frequency at baseline, and not for the full ITT population originating in Study 020. The frequency of nocturnal enuresis (i.e., number of dry nights/week) and the proportion of subjects continent at the end of treatment both improved at month 6 and were maintained at month 12. Categorization into one of five "improvement" categories at the end of treatment found 90% of those with data on this item rated their improvement between "minimal" and "100%," although assessed parental satisfaction with treatment showed that slightly fewer than half the parents felt their child had received "much benefit."

Subgroup analyses were conducted to explore the effect of age, gender and baseline weight on response to treatment. Greatest improvement was seen in children aged 5-7 years, females and those weighing < 20 kg; however, these subjects also had the highest frequency of baseline incontinence.

There were no deaths and few serious adverse events in this study. The overall frequency of adverse events was similar to that seen in the two placebo-controlled trials. The rate of anticholinergic side effects overall was low. Laboratory data were missing from over half of the population; however, no concerning signals were noted. ECG data were not assessed in this study.

Signals previously noted in Studies 020 and 008, regarding increased incidence of behavioral disorders and urinary tract infections in the tolterodine-treated subjects, remained of concern in this group, where 2% of subjects experienced abnormal and/or aggressive behavior group, and 7.4%

experienced UTIs, a figure about midway between that seen in the subjects who received 24 weeks of tolterodine in Studies 008 and 021, and higher than both placebo groups in the earlier studies.

APPENDIX C

16 CRITICAL ANALYSIS

The sponsor submitted two modules [*5.3.5.4.1* and *2.7.4*] to meet the two critical analyses requirements listed in the Written Request dated January 23, 2001. Information was obtained by review of the tolterodine clinical development program and MEDLINE and BIOSIS Previews searches on:

- All citations for "tolterodine"
- MESH search for "tolterodine" with "children," "cystometric measurement" and "urodynamic tests"

Section 2 of module 5.3.5.4.1 is entitled "Trials in which Urodynamic Assessments were Used in Adults" and is intended to fulfill the Written Request for "a critical analysis of urodynamic data in adults with overactive bladder treated with tolterodine." Section 3 of module 5.3.5.4.1 is entitled "Published Studies of Tolterodine in Children." Module 2.7.4 is entitled "Summary of Clinical Safety" and reports on safety results in 595 pediatric patients treated with tolterodine in eight completed clinical trials. The latter two submissions are jointly intended to fulfill the Written Request for "a critical analysis of tolterodine safety in pediatric patients based on data from clinical trials and published literature."

The review of trials in adults produced ten studies, nine by the sponsor, one by an investigator (see Table 107 and Table 108). Six of the eight sponsor studies of tolterodine IR were submitted in NDA 20-771 and the single study of tolterodine PR was submitted in NDA 21-228. Of the sponsor studies, one was a Phase 1 study of tolterodine IR in healthy males, which reported only descriptive data (90-081-00). There were five phase 2 studies on tolterodine IR in adults with detrusor hyperreflexia and detrusor instability (92-OATA-002, 003, 005, 006 & 023) – pooled data from four of the five studies show a significant dose-response relationship for volume at first detrusor contraction, maximum cystometric capacity and PVR urine volume; data from individual studies is inconsistent in significance. An additional Phase 2 study of tolterodine PR in adults with overactive bladder (OAB) (97-TOCR-002) found a significant dose-response relationship for PVR urine volume only. Two phase 3 studies on tolterodine IR were identified:

- one in adults with detrusor hyperreflexia and detrusor instability, which found a significant increase in volume at first detrusor contraction and maximum cystometric capacity in tolterodine 2 mg v. placebo, and in PVR urine volume in tolterodine 1 or 2 mg v. placebo (94-OATA-017)
- one in adults with OAB and bladder outlet obstruction, which found a significant increase in volume at first detrusor contraction, maximum cystometric capacity and in PVR urine volume in tolterodine 2 mg v. placebo, without adverse effect on urinary flow, detrusor muscle function or incidence of urinary retention (98-OATA-062)

Finally, one investigator-initiated study was identified, on tamsulosin (an alpha-blocker) with or without tolterodine IR in adults with detrusor instability and bladder outlet obstruction (Athanasopoulos et al, 2003). This study showed significant improvement in maximum unstable contraction pressure and volume at first unstable contraction in the group receiving both tamsulosin and tolterodine.

Table 107 Sponsor-Conducted Adult Trials Assessing Urodynamic Data

Study No Document No Author	Study Description	Duration/ Phase/ Formulation	Indication	Dosage/ Control	Number of Patients or Subjects*
92-OATA-002 94C0697 Jepsson [10]	A Phase II randomized, double-blind, placebo-controlled, parallel group, dose ranging multicenter study of the safety and efficacy of tolterodine in patients with detrusor instability	2 weeks 2 IR	Detrusor instability	Tolterodine 0.5 mg bid 1 mg bid 2 mg bid 4 mg bid Placebo	 21 16 15 16 13
92-OATA-003 96C0150 Jepsson [11]	A Phase II randomized, double-blind, placebo-controlled, parallel group, dose ranging multicenter study of the safety and efficacy of tolterodine in patients with detrusor hyperreflexia	2 weeks 2 IR	Detrusor hyperreflexia	Tolterodine 0.5 mg bid 1 mg bid 2 mg bid 4 mg bid Placebo	 14 16 19 14 19
93-OATA-005 96C0435 Kohrerstrand [12]	A Phase II randomized, double-blind, placebo-controlled, parallel group, dose ranging multicenter study of the safety and efficacy of tolterodine in patients with detrusor hyperreflexia	2 weeks 2 IR	Detrusor hyperreflexia	Tolterodine 0.5 mg bid 1 mg bid 2 mg bid 4 mg bid Placebo	 20 16 18 17 19
93-OATA-006 96C0436 Kohrerstrand [13]	A Phase II randomized, double-blind, placebo-controlled, parallel group, dose ranging multicenter study of the safety and efficacy of tolterodine in patients with detrusor instability	2 weeks (+2 weeks, optional) 2 IR	Detrusor instability	Tolterodine 0.5 mg bid 1 mg bid 2 mg bid 4 mg bid Placebo	 16 14 14 11 13
95-OATA-023 c011632 Wallenbeck [14]	A Phase II randomized, double-blind, placebo-controlled, parallel group, dose ranging multicenter study of K2234 (tolterodine) in patients with detrusor hyperreflexia or detrusor instability	4 weeks 2 IR	Detrusor instability or detrusor hyperreflexia	Tolterodine 0.5 mg bid 1 mg bid 2 mg bid Placebo	 59 55 60 59
94-OATA-017 96C0441 Steringer [15]	A Phase III randomized, double-blind, parallel group, multinational study of the safety and efficacy of tolterodine, compared to placebo, in patients with detrusor overactivity	4 weeks 3 IR	Detrusor overactivity	Tolterodine 1 mg bid 2 mg bid Placebo	 99 99 44

*Number randomized unless otherwise noted

Study No Document No Author	Study Description	Duration/ Phase/ Formulation	Indication	Dosage/ Control	Number of Patients or Subjects*
98-OATA-062 c0037716 Ekenas and Olofsson [16]	Safety and efficacy of tolterodine tablets in men with bladder overactivity and coexisting bladder outlet obstruction. A multinational, randomised, double blind and placebo-controlled 12 weeks study.	12 weeks 3b IR	Males with bladder overactivity and bladder outlet obstruction	Tolterodine 2 mg bid Placebo	 150 72
97-TOCR-002 c0003471 Strombom [17]	Dose effect trial of tolterodine prolonged release capsules. A double-blind, double-dummy, cross-over trial in patients with overactive bladder	7 days on each treatment 2 PR	Overactive bladder	Tolterodine PR 2, 4, 6, 8 mg qd IR 2 mg bid Placebo	58 total
90-081-00 91 96 394 Ekström [19]	The effect of Kabi 2234 on urinary bladder function after oral single-dose administration to healthy volunteers	1 dose 1 oral aqueous solution	None	6.4 mg	12†

*Number randomized, unless otherwise noted.
†Number included in analyses.
bid=twice a day; IR=immediate release; PR=prolonged release.

Source: Table 2, *5.3.5.4.1, pp 8-9*

Table 108 Published Adult Trials Assessing Urodynamic Data

Study Title	Study Type and Design	Comparator	Tolterodine Regimen (mg)	N	Patient Selection	Results and Comments on Urodynamic Parameters
Combination treatment with an α–blocker plus an anticholinergic for bladder outlet obstruction [2]	Randomized, open-label, parallel group, positive control	Tamsulosin 0.4 mg qd for 3 months	Tolterodine 2 mg bid + tamsulosin 0.4 mg qd for 3 months	50	Male patients with urodynamically proven mild/moderate bladder outlet obstruction and concomitant detrusor instability	Statistically significant differences between groups in bladder capacity and volume at 1st unstable contraction (both higher in combination group), and maximum unstable contraction pressure (lower in combination group). No statistically significant changes in PVR in either group.

Source: Table 3, *5.3.5.4.1, p 9*

Overall, a total of 1138 adult patients were studied in these ten trials. Pooled data from the four Phase 2 studies on tolterodine IR whose designs were similar suggested a positive dose-response relationship , with statistically significant dose-effect relationships seen for volume at first detrusor contraction, maximum cystometric capacity and PVR volume. The optimal dose was not identified due to small numbers of subjects and short treatment durations; however, 2 mg BID of tolterodine IR was described as both safe and efficacious.

Five pediatric studies were identified by the sponsor from the literature (See Table 109):

- A prospective open-label study of tolterodine IR in children with dysfunctional voiding who previously failed to tolerate oxybutynin, which found comparable efficacy and improved tolerability of tolterodine (Bolduc et al, 2003)
- An open-label, non-randomized parallel group of tolterodine IR vs. tolterodine PR vs. oxybutynin in children with non-neurogenic diurnal urinary incontinence and symptoms of OAB, which found tolterodine IR less efficacious than the 2 comparators in reduction of incontinence; oxybutynin more effective in complete resolution of incontinence; and no difference in rate of anticholinergic adverse effects (Reinberg et al, 2003)
- An open-label, non-randomized sequential dose-escalation study of tolterodine IR in children with OAB, in which only descriptive data was reported (13 of 33 had "possibly related" adverse effects, 2 withdrew due to adverse effects) (Hjalmas et al, 2001)
- A retrospective chart review of tolterodine IR in children with dysfunctional voiding, for which only descriptive data were reported (4 of 30 reported adverse effects, one withdrew due to adverse effects) (Munding et al, 2001)
- A prospective, non-randomized study of tolterodine IR in children with detrusor hyperreflexia, which found no significant difference between urodynamic effects of tolterodine vs. historical use of oxybutynin (Goessl et al, 2000)

Table 109 Pediatric Trials in the Published Literature

Study Title	Study Type and Design	Comparator	Tolterodine Regimen	N	Patient Selection	Results and Comments
The use of tolterodine in children after oxybutynin failure [20]	Prospective, open-label	None	Tolt IR 1 mg bid (n=12) and 2 mg bid (n=22) for up to 16 mos	34 F18 M16	Children with dysfunctional voiding who previously failed to tolerate oxybutynin	Median duration of tolterodine treatment: 11.5 mos. 20 patients reported no AEs. 6 described the same but tolerable AEs as with oxybutynin. 8 patients discontinued tolterodine because of AEs after a median of 5 mos treatment. Efficacy of tolterodine was comparable to that of oxybutynin: reduction in wetting episodes at 1 year was >90% in 23 patients (68%), >50% in 5 patients (15%) and <50% in 6 patients (18%)
Therapeutic efficacy of ER oxybutynin and IR and PR tolterodine in children with diurnal urinary incontinence [21]	Open-label, non-randomized, parallel group	Oxybutynin ER 5 mg qd titrated to response Duration of trt unknown	Tolt IR 2 mg/day titrated to response Tolt PR 2 mg/day titrated to response; Duration of trt unknown	132 F86 M46	Children with non-neurogenic diurnal urinary incontinence and symptoms of overactive bladder	Oxybutynin and tolterodine PR were significantly more effective at reducing daytime urinary incontinence than tolterodine IR ($p<0.01$ and $p<0.05$, respectively). Oxybutynin ER was significantly more effective than tolterodine PR for complete resolution of diurnal incontinence ($p<0.05$). No differences in the occurrence of anticholinergic AEs were seen among the treatment groups.

Study Title	Study Type and Design	Com-parator	Tolterodine Regimen	N	Patient Selection	Results and Comments
The overactive bladder in children: a potential future indication for tolterodine [22]	Open-label, non-randomized sequential, dose-escalation	None	0.5 mg bid (n=11); 1 mg bid (n=10), or 2 mg bid (n=12) for 14 days	33 F13 M20	Children with overactive bladder and symptoms of urgency, frequency and/or urge incontinence	PVR values unchanged after 2 wks of treatment for all three doses. AEs were reported by 20 patients (six on 0.5 mg, five on 1 mg, and nine on 2 mg). Most AEs were not considered to be drug-related; of the 13 possibly related events, 10 occurred in patients taking 2 mg. Headache was the most common AE. Two patients withdrew due to AEs (tachycardia and problems with visual accommodation). Improvement seen in voiding diary variables in all treatment groups after 2 wks of treatment; efficacy was greatest in patients taking 1 mg and 2 mg bid.
Use of tolterodine in children with dysfunctional voiding: an initial report [23]	Retrospective chart review	None	Tolt IR 1 mg bid (n=1), tolt IR 2 mg bid (n=27), or tolt IR 4 mg bid (n=2) for an average of 5.2 mos (range 1-14 mos)	30 F23 M7	Pediatric patients with a primary diagnosis of dysfunctional voiding	Wetting episodes were cured in 10 patients, and improved in 12 patients; 8 patients failed to show improvement. Four patients reported side effects (2 con-stipation, 1 dry mouth, and 1 diarrhea); one patient discontinued tolterodine IR treatment due to diarrhea.
Efficacy and tolerability of tolterodine in children with detrusor hyperreflexia [24]	Prospective, non-randomized	None	0.1 mg/kg orally daily, divided into 2 doses for up to 3 mos	22 F10 M12	Children with detrusor hyperreflexia: Group 1: no previous trt (n=12); Group 2: previous oxybutynin treatment (n=10)	In Group 1, significant increases in maximum bladder capacity and detrusor compliance, and a significant decrease in maximum detrusor pressure, were seen. In Group 2, no significant differences in the urodynamic effects of oxybutynin versus tolterodine were seen. Only 1 AE (transient facial flushing after 1st dose) was seen. Notably, no AEs reported in the 6 children in Group 2 who had AEs during previous oxybutynin treatment.

Source: Table 16, *5.3.5.4.1, pp 43-44*

Medical Officer's Comments:

1) **The rationale for placing PK data for the immediate release formulation in the Detrol LA label is unclear.**

2) **This statement is based upon a comparison of data from Study 044 to adult data in the Detrol immediate release label. While this statement appears true (see Table 4 and Table 5 in this review) for C_{max}, it would be helpful to present the adult data to which the pediatric parameters are compared. Data for C_{avg} are not provided; however, AUC (on which C_{avg} is based) for children can be described as equivalent to, slightly lower than or slightly greater than that seen in adults, depending on which adult dataset is referenced.**

3) **It should be noted that AUC and C_{max} estimates based on Study 044 were found to be consistently higher than the three other pediatric studies using equivalent oral doses (Studies 002, 008 and 020).**

   The elimination half-life appeared prolonged in pediatric patients 11 to 15 years of age as compared to the adult population. However, C_{avg}, C_{max} and t_{max} were comparable between the two populations at the 4-mg daily dose.

Medical Officer's Comment:

This statement is based upon a comparison of combined data from Studies 003 and 018 with Table 1 in the current Detrol LA label.

In patients ranging in age from 1 month to 4 years who received a 0.030 mg/kg twice-daily dose of an investigative tolterodine tartrate oral solution, tolterodine oral clearance (4.9 ± 4.5 L/h/kg) was higher and elimination half-life (1.5 ± 0.6 h) was shorter than values observed in children 5 to 10 years of age (CL/F = 3.7 ± 3.6 L/h/kg; $t_{1/2}$ = 2.2 ± 1.0 h).

Medical Officer's Comment:

There is no utility to placing PK data in the Detrol LA label that concerns an immediate release formulation that is not commercially available.

Evaluation of the pharmacokinetic/pharmacodynamic relationship in children based on active moiety AUC suggests that administration of a tolterodine daily dose of 2 mg for patients weighing ≤35 kg or 4 mg for patients with body weight >35 kg would provide active moiety exposure that is similar to that in adults receiving 4 mg daily.

Medical Officer's Comments:

1) **Inclusion of suggested dosing recommendations suggests an implied indication for the use of tolterodine in the pediatric population, which is not supported by the efficacy data. Even if efficacy had been demonstrated, due to the confounding of age and weight in the population PK analysis, it is not yet possible to make dose recommendations.**

2) **It is the opinion of the reviewer that inclusion of pharmacokinetic data and the five paragraphs suggested by the sponsor would imply efficacy of tolterodine in the pediatric population. It is recommended that the sponsor's proposed additions be rejected and the current statement, which the sponsor proposed to delete, be retained.**

3) **The recommendation from the Division of Drug Marketing, Advertising and Communications (DDMAC) states that "DDMAC recommends deletion of the pediatric studies in the Pharmacokinetics in Special Populations, Clinical Studies, and Adverse Reactions sections of the PI in order to avoid an implied effectiveness in the pediatric patient population that has not been demonstrated."**

17.1.1 Sponsor Proposed Addition of Pediatric Patients Subsection to CLINICAL STUDIES Section

The sponsor proposes to add the following Pediatric Patients Subsection:

> DETROL LA 2 mg was evaluated in pediatric patients 5 to 10 years of age with the symptoms of urinary urgency, frequency and urge incontinence in two randomized, multicenter, placebo-controlled, double-blind, 12-week studies. A total of 487 patients received DETROL LA 2 mg in the morning and 224 received placebo. Efficacy in this population has not yet been demonstrated.

Medical Officer's Comments:

1) **The statement that efficacy has not "yet" been demonstrated is inappropriate. If there were to be any statement regarding clinical studies conducted in children, nothing more than a general description of the findings should be given. It is recommended that such a description be placed in the PRECAUTIONS Section.**
2) **The recommendation from the Division of Drug Marketing, Advertising and Communications (DDMAC) states that "DDMAC recommends deletion of the pediatric studies in the Pharmacokinetics in Special Populations, Clinical Studies, and Adverse Reactions sections of the PI in order to avoid an implied effectiveness in the pediatric patient population that has not been demonstrated."**

17.1.2 Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection

The sponsor proposes to delete the following sentence:

> *The safety and effectiveness of tolterodine in pediatric patients has not been established.*

And replace it with the following four sentences:

> The safety of DETROL LA has been demonstrated in two Phase 3 placebo-controlled, double-blind, 12-week studies of 486 pediatric patients ages 5 to 10. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults. The overall safety profile of tolterodine in this age group was comparable to that seen in adults (see **Clinical Studies** and **Adverse Reactions**).

Medical Officer's Comments:

1) **Given that there is off-label use in children of both Detrol and Detrol LA, there may be value in providing adverse event information obtained from the two phase 3 studies. The following wording is suggested:**

> "Efficacy in the pediatric population was not demonstrated.
>
> A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5 to 10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with

urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients receiving placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA as compared to 0.9% of children treated with placebo."

2) **The recommendation from DDMAC states that "DDMAC recommends inclusion of the important safety information from these clinical studies in the Precautions-Pediatric Use section only, if clinically relevant, and including a prominent and concise statement about Detrol LA's ineffectiveness in this patient population. For example, 'The effectiveness of Detrol LA in children has not been demonstrated.'"**

3) **An additional comment from DDMAC is "Can the safety information in the Precautions-Pediatric Use section be qualified, i.e., 'The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults.' Terms such as "higher," "mild or moderate," and "lower" are vague and require context. This information would be useful to the reader."**

17.1.3 Sponsor Proposed Addition of Pediatric Studies Subsection to ADVERSE REACTIONS Section,

The sponsor proposes to add the following Pediatric Studies Subsection:

In two placebo-controlled clinical trials of DETROL LA Capsules, 710 pediatric patients ages 5 to 10 years were treated with DETROL LA (n=486) or placebo (n=224). Patients were treated with DETROL LA 2 mg for 12 weeks. The overall frequency of adverse experiences was almost identical in the DETROL LA and placebo treatment groups (48% and 49%, respectively). Urinary tract infection was the most common adverse event occurring at a rate greater than placebo reported by pediatric patients receiving DETROL LA. Dry mouth was only reported in 0.8% of patients treated with DETROL LA and in 1.8% of patients receiving placebo. A serious adverse event was reported by 1% (n=6) of pediatric patients receiving DETROL LA and 1% (n=2) of patients receiving placebo.

The frequency of discontinuation due to adverse events was 3% for both the DETROL LA and placebo treatment groups. Table 5 lists the adverse events reported in 1% or more of pediatric patients treated with DETROL LA 2 mg once daily in the 12-week studies.

Table 5 Incidence* (%) Of Adverse Events Exceeding Placebo Rate and Reported In ≥1% of Pediatric Patients Treated With DETROL LA (2 mg once daily) in Two 12-Week, Phase 3 Clinical Trials

Body System	Adverse Event	%DETROL LA (n=486)	%Placebo (n=224)
Gastrointestinal disorders	Abdominal pain	5	3
	Vomiting	4	2
	Diarrhea	3	1
	Constipation	2	1
Infections and infestations	Urinary tract infection	7	4
	Ear infection	1	0
Psychiatric disorders	Abnormal behavior	2	0
Respiratory, thoracic, and mediastinal disorders	Rhinitis	2	0

*in nearest integer.

Medical Officer's Comment:

The reviewer proposes that this section remain absent from the DETROL LA label.

17.1.4 Sponsor Proposed Changes to Revision date

The sponsor proposes to change the revision date listed at the very end of the physician insert from:

Revised July 2003

818 229 006

To:

Revised Month Year

Medical Officer's Comment:

The proposed changes are acceptable to the reviewer.

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[1] Raes A et al, Retrospective analysis of efficacy and tolerability of tolterodine in children with overactive bladder. Eur Urol 45: 240-44, 2004

[2] Nijman RJ, Role of antimuscarinics in the treatment of nonneurogenic daytime urinary incontinence in children. Urology 63: 45-50, 2004

[3] Johnson, K The Harriet Lane Handbook, p 101, Mosby, St. Louis, MO, 1993

[4] Garson A, How to measure the QT interval – what is normal? Am J Cardiol 72: 14B-16B, 1993

[5] Johnson, K The Harriet Lane Handbook, p 101, Mosby, St. Louis, MO, 1993

[6] Two placebo subjects were age 4 and one age eleven.

Medical Officer's Pediatric Exclusivity Memo

To:	Pediatric Exclusivity Board
Through:	George Benson, MD Team Leader, HFD-580
From:	Lisa M. Soule, MD Medical Officer, HFD-580
Date:	December 22, 2003
Re:	NDA 21-228 SE8-006 Detrol LA® (Tolterodine tartrate) Pfizer Inc. Correspondence Date: October 10, 2003 Date Received: October 14, 2003

Current submission:

A Written Request (WR) letter dated January 23, 2001, asked Pfizer Inc. to perform four pediatric studies with tolterodine tartrate and to prepare two critical analyses. In the current electronic submission **SE8-006**, the sponsor has responded to the WR by submitting:

- a final study report, 583E-URO-0581-001 (Study #1 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in 8 patients ages one month to 4 years, with detrusor hyperreflexia due to neurogenic conditions),

- a final study report, 583E-URO-0581-002 (Study #2 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in approximately 15 patients ages five to ten years, with detrusor hyperreflexia due to neurogenic conditions),

- a final study report, 583E-URO-0581-003 (Study #3 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in approximately 15 patients ages eleven to fifteen years, with detrusor hyperreflexia due to neurogenic conditions),

- three final study reports, 583E-URO-0084-020, DETAPE-0581-008 and 583E-URO-0084-021 [Study #4 in the Written Request, a 12-week double-blind, two parallel group, placebo-controlled randomized clinical efficacy, pharmacokinetic and safety study with a minimum 12-week safety extension study in approximately 300 patients (to ensure a minimum of 100 patients completing 24 weeks of treatment) ages five to ten years, with overactive bladder], and

- two critical analyses.

Reviewer's comment:
The submitted material is adequate to meet the requirements of the Written Request for each of the four studies and the critical analyses. Please see the five attached Pediatric Exclusivity Determination Templates for specific details (Attachments A - E).

While the Sponsor does not submit labeling language specific to the pediatric population in the "Indications and Usage" section nor under the "Dosage and Administration" section of the labeling, as described in 21 CFR 201.57(f) (9), it appears to the reviewer that there is an implied pediatric indication sought, as evidenced by submission of pediatric PK data and language in the "Pediatric Use" section of the labeling. This will be a review issue.

Recommendation:
1) Recommend granting pediatric exclusivity for NDA 21-228 SE8-006.

cc: Original NDA 21,228
HFD-580: D. Griebel, G. Benson, B. Gierhart, L. Soule, and J. King

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Soule
12/23/03 10:39:29 AM
MEDICAL OFFICER

George Benson
12/23/03 11:10:51 AM
MEDICAL OFFICER

ATTACHMENT A

Study 1 Pediatric Exclusivity Determination Template

Written Request Item – January 23, 2001	Information Submitted	Condition Met
Types of Studies/Study Design: Study 1: Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]) & safety study Study Design: Repeated dose, multiple dose-level, open label, minimum 2 week duration, PK, PD and safety study Objectives: 1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of Detrol™ (tolterodine tartrate) syrup to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine. 2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions. 3. To evaluate the effect and safety of Detrol ™ (tolterodine tartrate) syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.	**Types of Studies:** Study 1: Study 583E-URO-0581-001 Phase I/II, open label, dose escalating PK, PD (urodynamic) and clinical effect and safety study. Duration of treatment 12 weeks (4 at each dose) *5.3.4.2.1, p4* Objectives: *5.3.4.2.1, p3* Primary: To collect data as the basis for a dosage recommendation for tolterodine in children 1 month to 4 years of age with neurogenic lower urinary tract dysfunction. This recommendation was to be based on a comparison of the PK of the active moiety (sum of unbound tolterodine and DD 01) with data from studies in adults and children 5-10 years old. Secondary: To estimate the PK variables for tolterodine and DD 01, and assess the PD (urodynamic) and clinical effect and safety of tolterodine oral solution given in doses of 0.03, 0.06 and 0.12 mg/kg/day in patient from 1 month to 4 years of age with neurogenic lower urinary tract dysfunction. Data were collected to determine a tolterodine dose-PD effect and **tolterodine/DD 01 (active moiety) concentration-PD effect relationship** with urinary storage parameters of volume and compliance.	**Design: Yes** *5.3.4.2.1, p4* **Objective 1: Yes** *5.3.4.2.1, p7, 57-58* **Objective 2: Yes** *5.3.4.2.1, p62-70* Concentration-effect was described for active moiety only; however, this is acceptable to the Division's Clinical Pharmacologists **Objective 3: Yes** *5.3.4.2.1, p49-89*

Indication(s) to be studied: **Study 1:** Detrusor hyperreflexia due to neurogenic conditions	**Indications Studied:** **Study 1:** Detrusor hyperreflexia *5.3.4.2.1, p4* [See also entry criteria *5.3.4.2.1, p4*]	**Yes** *5.3.4.2.1, p23-24, 52-54*
Age group & population in which study will be performed: **Study 1:** Ages one month to 4 years	**Age group & population in which study was performed:** **Study 1:** One month to 4 years *5.3.4.2.1, p4* Actual age range: 0.3 to 4.9 years; *5.3.4.2.1, p101* Age groups: 0 - 6 mos: N=3; 6 mos – 2 yrs: N=6; 2-4 years: N=10 *5.3.4.2.1, p7*	**Yes** *5.3.4.2.1, p101*
Number of patients to be studied or power of study to be achieved: **Study 1:** Enroll a sufficient number of patients to adequately characterize the PK/PD parameters. PK/PD parameters must be obtained on a minimum of eight patients; with at least three of these patients being less than 6 months of age.	**Number of patients studied or power achieved:** **Study 1:** Safety population: N=19; PK population: N=17 *5.3.4.2.1, p4* Gender breakdown: 10 M, 9 F. *5.3.4.2.1, p7* Racial breakdown: 16 white, 1 black, 2 unspecified *5.3.4.2.1, p7* Two pts withdrew (1 due to AE, 1 withdrew consent due to frequent UTIs). One <6 mos old pt had major protocol violation (did not require intermittent catheterization) *5.3.4.2.1, p49-50* One pt counted in the PK population did not have his data used except in figures, as he was incorrectly dosed on the day of sampling. PK age breakdown: 0 - 6 mos: N=3; 6 mos – 2 yrs: N=5; 2-4 years: N=8. PK data missing on 3 pts: 4 y/o who withdrew; 4 y/o who had multiple unsuccessful sticks, a 10 month old *5.3.4.2.1, p49-52*	**Yes** *5.3.4.2.1, p4, 7, 49-52*

Entry criteria: **Study 1:** Not specified	**Entry criteria used:** **Study 1:** Male & female 1 month to 4 years of age, inclusive. Stable neurological disease (myelomeningocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management or urinary drainage. Body weight or BMI within normal range (between the 5th-95th percentiles), according to the CDC Growth and BMI charts for the US *5.3.4.2.1, p4*	**N/A**
Clinical endpoints: **Study 1:** 1. PK: appropriate analysis of tolterodine & DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group. 2. PD: appropriate urodynamic evaluation. Evaluations may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions. 3. Dose-response: characterization of dose (in mg/kg)-effect (urodynamic) and concentration-effect (urodynamic)	**Clinical endpoints used:** **Study 1:** *5.3.4.2.1, p5* 1. PK parameters for the active moiety (defined as the sum of the unbound tolterodine and DD 01 concentrations) including **serum** AUC_{0-12}, C_{max} and C_{min}. PK parameters for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12} (F_{ext}), C_{max}, the time of occurrence of C_{max} (t_{max}), C_{min} and apparent terminal half-life ($t_{1/2,z}$). For tolterodine, oral steady-state volume of distribution (V_{ss}/F) and oral clearance (CL/F) 2. Clinical effects: volume to first detrusor contraction of magnitude >10 cm H_2O pressure, functional bladder capacity and leak point pressure, intravesical volume at 20 and 30 cm H_2O pressure, maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure), and bladder compliance (defined as delta volume/delta pressure) all measured at each dose level. Also, tolterodine dose-PD effects were determined by the assessment of urodynamic parameters at each dose	**1. Yes** Sponsor reports serum, not plasma values; this is acceptable to the Division's Clinical Pharmacologists. *5.3.4.2.1, p55* **2&3. Yes** Concentration-effect was described for active moiety only; however, this is acceptable to the Division's

	level. **Active moiety concentration-PD effects** were determined by the assessment of urodynamic parameters at the PK dose (0.06 mg/kg/day). Patient diary (clinical effect) variables included: mean number of catheterizations/micturitions per 24 hours, mean volume per catheterization/micturition and mean number of incontinence episodes per 24 hours, all at each dose level.	Clinical Pharmacologists *5.3.4.2.1, p34, 62-72*
4. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters 5. Safety: number of patients terminated prematurely	3. Safety – Hematology and serum chemistry tests, ECGs, GI function assessment and adverse events 4. Health economics – health care utilization data were collected throughout the trial. These data will contribute to an estimate of the direct costs of detrusor hyperreflexia in these patients.	**4. Yes** *5.3.4.2.1, p73-85*
Timing of assessments: if appropriate **Study 1:** For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with tolterodine.	**Timing of assessments:** **Study 1:** Washout of 6-14 days prior to baseline visit. First patient diary completed after at least three days washout, and over three days prior to the baseline visit. Urodynamics, patient diary, safety data (including assessment of GI function, ECGs, clinical laboratory results and AEs and health care utilization data) collected every four weeks, after completion of each dose level. PK data collected following the 0.06 mg/kg/d dose level only. *5.3.4.2.1, p4*	**Yes** *5.3.4.2.1, p28*
Drug specific safety concerns: **Study 1:** Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.	**Drug specific safety concerns evaluated:** **Study 1:** No deaths, no serious AEs; 1 pt withdrew consent, 1 withdrawn due to increased AST, considered related. No clinically significant changes in ECG or lab parameters. Constipation in 5 pts; no dry mouth; no dose-AE relationship.	**Yes** *5.3.4.2.1, p8*

Drug information: **Study 1: Amended August 5, 2002** • **Route of administration:** Oral • **Dosage:** Sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks • **Regimen:** Daily, in divided doses • **Formulation:** Tolterodine syrup (not commercially available)	**Drug information:** **Study 1:** *5.3.4.2.1, p4* • **Route of administration:** Oral • **Dosage:** Doses 0.03, 0.06 and 0.12 mg/kg/day, escalating every 4 weeks • **Regimen:** Daily, in divided doses • **Formulation:** Tolterodine L-tartrate oral solution (1 mg/5 ml)	**Yes** *5.3.4.2.1, p4, 28*
Statistical information (statistical analysis of the data to be performed): **Study 1:** 1. PK: descriptive analysis to include reporting of AUC, C_{max}, & C_{min} for tolterodine and DD 01 2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment.	**Statistical information (statistical analysis of the data performed):** **Study 1:** *5.3.4.2.1, p6* All patients who received study drug were included in the safety analysis. PK variables were summarized using descriptive statistics. Serum concentration profiles were presented graphically. PK variables were compared (informally) with similar variables from PK studies in adults and in children 5-10 years old without neurological compromise. Relationships of interest such as AUC by age, weight and BMI were investigated. Descriptive statistics for clinical effect variables were calculated by dose period, along with descriptive statistics for changes and percentage changes from baseline in these variables. Hodges-Lehman estimates and non-parametric 95%	**1. Yes** *5.3.4.2.1, p6,7* **2. Yes** *5.3.4.2.1, p7, 62-66*

	confidence intervals were calculated for these estimates. Volume based urodynamic variable were also calculated as values normalized to theoretical bladder capacity (%) and descriptive statistics for these normalized values were presented. The scoring of incontinence was summarized in frequency tables by dose period. Graphic presentations of the dose-effect relationship and the active moiety concentration-effect relationship for the clinical effect variables were evaluated.	
3. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.	Adverse events were coded according to the MedDRA and summarized in frequency tables by dose period. The frequency of laboratory test results that were outside the normal range and the frequency of abnormal ECGs were summarized by dose period. Means were calculated for each ECG variable for each series of measurements at each dose period. The change from baseline was also calculated for each ECG variable by dose period. Frequencies of QT, QTcF and QTcB intervals and changes from baseline in QT, QTcF and QTcB intervals that exceeded defined cut-off points were determined. Plots of changes in QTcF versus serum concentrations of tolterodine and DD 01 and versus AUC_{0-12} for tolterodine and DD 01 were examined for possible relationships. Assessments of GI function were summarized by dose period in frequency tables.	**3. Yes** *5.3.4.2.1, p6, 35, 73-85*
Labeling that may result from the studies: <u>**Study 1:**</u> Appropriate changes to the label to incorporate the study results will be made.	**Did the sponsor submit proposed labeling?** Not for this formulation.	**No labeling submitted for this formulation, which is not currently marketed.**

Format of reports to be submitted: A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guidelines for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports submitted:** Final study report format was acceptable.	**Yes**
Timeframe for submitting reports of the studies: Amended March 3, 2003 On or before October 15, 2003	**Date study reports were submitted:** October 14, 2003	**Yes**
Additional information:	**Conclusions:** *5.3.4.2.1, p 9* **Study 1:** Drug exposure, as measured by AUC and C_{max} of the active moiety, similar to that previously observed in 5-10 year olds w/OAB receiving 0.5 mg IR BID and slightly less than half that reported in adults receiving 2 mg IR BID. No apparent concentration-effect relationship. A dose-effect relationship was observed for urodynamic and micturition diary parameters, with the intermediate and highest doses showing the largest effects and the lowest dose showing no notable effect. Specifically, improvement from baseline was seen in: • Volume to first detrusor contraction at the 0.12 mg/kg/d dose, • Functional bladder capacity at the 0.06 mg/kg/d dose, • Intravesical volume at 20 cm H_2O at the 0.06 and 0.12 mg/kg/d doses, although the change was greater at the 0.06 mg/kg/d dose,	**N/A**

	• Mean number of incontinence episodes per 24 hours, in a dose-response manner at the 0.06 and 0.12 mg/kg/d doses and • Mean volume per catheterization/micturition, in a dose-response manner at the 0.06 and 0.12 mg/kg/d doses. 95% confidence limits included 0 for change in mean number of catheterizations/micturitions per 24 hours. Generally well tolerated, no new safety concerns identified.	

ATTACHMENT B

Study 2 Pediatric Exclusivity Determination Template

Written Request Item – January 23, 2001	Information Submitted	Condition Met
Types of Studies/Study Design: Study 2: Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]) & safety study Study Design: Repeated dose, multiple dose-level, open label, minimum 2 week duration, PK, PD and safety study. Objectives: 1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of tolterodine tartrate syrup to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine. 2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions. 3. To evaluate the effect and safety of tolterodine tartrate syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.	**Types of Studies:** Study 2: Study 583E-URO-0581-002 Phase I/II, open label, dose escalating PK, PD (urodynamic) and clinical effect and safety study. *5.3.4.2.2, p3* Duration of treatment 12 weeks (4 at each dose) *5.3.4.2.2., p4* Objectives: *5.3.4.2.2, p3* Primary: To collect data as the basis for a dosage recommendation for tolterodine in children 5 to 10 years of age afflicted with neurogenic lower urinary tract dysfunction. This recommendation was to be based on a comparison of the PK of the active moiety (sum of unbound tolterodine and DD 01) with data from studies in adults and children 5-10 years old. Secondary: To estimate the PK variables for tolterodine and DD 01, and assess the PD (urodynamic) and clinical effect and safety of tolterodine oral solution given in doses of 0.03, 0.06 and 0.12 mg/kg/day in patient from 5-10 years of age with neurogenic lower urinary tract dysfunction. Data were collected to determine a tolterodine dose-PD effect and **tolterodine/DD 01 (active moiety) concentration-PD effect relationship** with urinary storage parameters of volume and compliance.	**Design: Yes** *5.3.4.2.2, p3, 4* **Objectives:** **1. Yes** *5.3.4.2.2,p7, 54-7* **2. Yes** *5.3.4.2.2,p57-72* Concentration-effect was described for active moiety only; however, this is acceptable to the Division's Clinical Pharmacologists **3. Yes** *5.3.4.2.2,p68-89*

Indication(s) to be studied: **Study 2:** Detrusor hyperreflexia due to neurogenic conditions	**Indications Studied:** **Study 2:** Detrusor hyperreflexia *5.3.4.2.2, p3* [See also entry criteria *5.3.4.2.2, p4*]	**Yes** *5.3.4.2.2, p22, 51*
Age group & population in which study will be performed: **Study 2:** Ages five to ten years	**Age group & population in which study was performed:** **Study 2:** 5-10 years, inclusive *5.3.4.2.2, p4*	**Yes** *5.3.4.2.2, p22-23,100*
Number of patients to be studied or power of study to be achieved: **Study 2:** Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.	**Number of patients studied or power achieved:** **Study 2:** 15. *5.3.4.2.2., p4* Gender breakdown: 7 M, 8 F. *5.3.4.2.2, p6* Racial breakdown: 11 white, 4 black. *5.3.4.2.2, p6* Age distribution: 7 were 5-7 y/o, 8 were "8-11" [No pt was 11 or older at enrollment] *5.3.4.2.2, p6* PK age breakdown: 5-7 years: N=7; 8-10 yrs: N=6 *5.3.4.2.2, p49, 51, 100* (2 pts excluded from PK data due to incorrect dosing on the PK day.)	**Yes** *5.3.4.2.2, p6, 49, 51, 100*
Entry criteria: **Study 2:** Not specified	**Entry criteria used:** **Study 2:** Male & female 5-10 years of age, inclusive. Stable neurological disease (myelomeningocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management or urinary drainage. Body weight or BMI within normal range (between the 5^{th}-95^{th} percentiles), according to the CDC Growth and BMI charts for the US *5.3.4.2.2, p4*	**N/A**

Clinical endpoints:	**Clinical endpoints used:**	
<u>Study 2:</u> 1. PK: appropriate analysis of tolterodine & DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group.	<u>Study 2:</u> *5.3.4.2.2, p5* 1. PK parameters for the active moiety (defined as the sum of the unbound tolterodine and DD 01 concentrations) including **serum** AUC_{0-12}, C_{max} and C_{min}. PK parameters for tolterodine and DD 01, including AUC_{0-12}, the extrapolated fraction of the AUC_{0-12} (F_{ext}), C_{max}, the time of occurrence of C_{max} (t_{max}), C_{min} and apparent terminal half-life ($t_{1/2,z}$). For tolterodine, oral steady-state volume of distribution (V_{ss}/F) and oral clearance (CL/F)	**1. Yes** Sponsor reports serum, not plasma values; this is acceptable to the Division's Clinical Pharmacologists. *5.3.4.2.2, p54-57*
2. PD: appropriate urodynamic evaluation. Evaluations may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions. 3. Dose-response: dose (in mg/kg)-effect (urodynamic) and concentration-effect (urodynamic) 4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinent episodes per day	2. Clinical effects: volume to first detrusor contraction of magnitude >10 cm H_2O pressure, functional bladder capacity and leak point pressure, intravesical volume at 20 and 30 cm H_2O pressure, maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure), and bladder compliance (defined as delta volume/delta pressure) all measured at each dose level. Also, tolterodine dose-PD effects were determined by the assessment of urodynamic parameters at each dose level. **Active moiety concentration-PD effects** were determined by the assessment of urodynamic parameters at the PK dose (0.06 mg/kg/day). Patient diary (clinical effect) variables included: mean number of catheterizations/micturitions per 24 hours, mean volume per catheterization/micturition and mean number of incontinence episodes per 24 hours, all at each dose level.	**2-4. Yes.** *5.3.4.2.2, p60-72* Concentration-effect was described for active moiety only; however, this is acceptable to the Division's Clinical Pharmacologists.
5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters	3. Safety – Hematology and serum chemistry tests, ECGs, GI function assessment and adverse events	**5-6. Yes** *5.3.4.2.2, p72-83*

6. Safety: number of patients terminated prematurely	4. Health economics – health care utilization data were collected throughout the trial. These data will contribute to an estimate of the direct costs of detrusor hyperreflexia in these patients.	
Timing of assessments: if appropriate **Study 2:** For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with tolterodine.	**Timing of assessments:** **Study 2:** Washout of 6-14 days prior to baseline visit. First patient diary completed after at least three days washout, and over three days prior to the baseline visit. Urodynamics, patient diary, safety data (including assessment of GI function, ECGs, clinical laboratory results and AEs and health care utilization data) collected every four weeks, after completion of each dose level. PK data collected following the 0.06 mg/kg/d dose level only. *5.3.4.2.2., p4*	**Yes** *5.3.4.2.2, p27*
Drug specific safety concerns: **Study 2:** Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.	**Drug specific safety concerns evaluated:** **Study 2:** No withdrawals, deaths, serious AEs. No clinically significant changes in ECG or lab parameters. Constipation most common; no dry mouth, 1 abd pain; no dose-AE relationship. *5.3.4.2.2, p8*	**Yes** *5.3.4.2.2, p8, 72*
Drug information: **Study 2: Amended August 5, 2002** • **Route of administration:** Oral • **Dosage:** Sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks	**Drug information:** **Study 2:** *5.3.4.2.2, p4* • **Route of administration:** Oral • **Dosage:** Doses 0.03, 0.06 and 0.12 mg/kg/day, escalating every 4 weeks	**Yes** *5.3.4.2.2, p4, 23*

• **Regimen:** Daily, in divided doses • **Formulation:** Tolterodine syrup (not commercially available)	• **Regimen:** Daily, in divided doses • **Formulation:** Tolterodine L-tartrate oral solution (1 mg/5 ml)	
Statistical information (statistical analysis of the data to be performed): **<u>Study 2:</u>** 1. PK: descriptive analysis to include reporting of AUC, C_{max}, & C_{min} for tolterodine and DD 01 2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment. 3. Diary: number of micturitions per 24 hours and number of incontinence episodes per day (diary data) to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.	**Statistical information (statistical analysis of the data performed):** **<u>Study 2:</u>** *5.3.4.2.2, p6* All patients who received study drug were included in the safety analysis. PK variables were summarized using descriptive statistics. Serum concentration profiles were presented graphically. PK variables were compared (informally) with similar variables from PK studies in adults and in children 5-10 years old without neurological compromise. Relationships of interest such as AUC by age, weight and BMI were investigated. Descriptive statistics for clinical effect variables were calculated by dose period, along with descriptive statistics for changes and percentage changes from baseline in these variables. Hodges-Lehman estimates and non-parametric 95% confidence intervals were calculated for these estimates. Volume based urodynamic variable were also calculated as values normalized to theoretical bladder capacity (%) and descriptive statistics for these normalized values were presented. The scoring of incontinence was summarized in frequency tables by dose period. Graphic presentations of the dose-effect relationship and the active moiety concentration-effect relationship for the clinical effect variables were evaluated.	**1. Yes** *5.3.4.2.2, p6* **2. Yes** *5.3.4.2.2, p7* **3. Yes** *5.3.4.2.2, p7*

4. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.	Adverse events were coded according to the MedDRA and summarized in frequency tables by dose period. The frequency of laboratory test results that were outside the normal range and the frequency of abnormal ECGs were summarized by dose period. Means were calculated for each ECG variable for each series of measurements at each dose period. The change from baseline was also calculated for each ECG variable by dose period. Frequencies of QT, QTcF and QTcB intervals and changes from baseline in QT, QTcF and QTcB intervals that exceeded defined cut-off points were determined. Plots of changes in QTcF versus serum concentrations of tolterodine and DD 01 and versus AUC_{0-12} for tolterodine and DD 01 were examined for possible relationships. Assessments of GI function were summarized by dose period in frequency tables.	**4. Yes** *5.3.4.2.2, p8, 74, 75*
Labeling that may result from the studies: <u>Study 2:</u> Appropriate changes to the label to incorporate the study results will be made.	**Did the sponsor submit proposed labeling?** Not for this formulation.	**No labeling submitted for this formulation, which is not currently marketed.**
Format of reports to be submitted: A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guidelines for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports submitted:** Final study report format was acceptable.	**Yes**

Timeframe for submitting reports of the studies: Amended March 3, 2003 On or before October 15, 2003	**Date study reports were submitted:** October 14, 2003	**Yes**
Additional information:	**Conclusions:** *5.3.4.2.2, p 8* <u>Study 2:</u> Drug exposure, as measured by AUC and C_{max} of the active moiety, similar to that previously observed in children w/OAB receiving 0.5 mg IR BID and approximately half that reported in adults receiving 2 mg IR BID. No apparent concentration-effect relationship was demonstrated. A dose-effect relationship was observed for urodynamic and micturition diary parameters, with the low and intermediate doses demonstrating similar effects and the highest dose showing the largest effect. Specifically, dose-related improvements were seen in: • volume to first detrusor contraction, • intravesical volume at 20 cm H_2O and • mean number of incontinence episodes per 24 hours. 95% confidence limits that included a change of 0 were seen for: • change in functional bladder capacity, • mean # catheterizations/micturitions per 24 hours and • mean volume per catheterization/micturition. Generally well tolerated, no new safety concerns identified.	**N/A**

ATTACHMENT C

Study 3 Pediatric Exclusivity Determination Template

Written Request Item – January 23, 2001	**Information Submitted**	**Condition Met**
Types of Studies/Study Design: Study 3: Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]) & safety study Study Design: Repeated dose, multiple dose-level, open label, minimum 2 week duration, PK, PD and safety study Objectives: 1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of tolterodine tartrate extended release capsules to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine. 2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.	**Types of Studies:** Study 3: Study 583E-URO-0581-003 Phase I/II, open label, dose escalating PK, PD (urodynamic) and clinical effect and safety study. *5.3.4.2.3, p3* Duration of treatment 12 weeks (4 at each dose) *5.3.4.2.3., p4* Objectives: *5.3.4.2.3, p4* Primary: To collect data as the basis for a dosage recommendation for tolterodine in children 11 to 15 years of age afflicted with neurogenic lower urinary tract dysfunction. This recommendation was to be based on a comparison of the PK of the active moiety (sum of unbound tolterodine and DD 01) with data from studies in adults and children 5-15 years old. Secondary: To estimate the PK variables for tolterodine and DD 01, and assess the PD (urodynamic) and clinical effect and safety of tolterodine PR capsules, given in doses of 2, 4 and 6 mg/day in patient from 11 to 15 years of age. Data were collected to determine a tolterodine dose-PD effect and **tolterodine/DD 01 (active moiety) concentration-PD effect relationship** with urinary storage parameters of volume and compliance.	**Design: Yes** *5.3.4.2.3, p3, 4* **Objectives:** **1. Yes** *5.3.4.2.3, p4, 51-57* **2. Yes** *5.3.4.2.3, p4, 58-70* Concentration-effect was described for active moiety only; however, this is acceptable to the Division's Clinical Pharmacologists

3. To evaluate the effect and safety of tolterodine tartrate extended release capsules in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.		**3. Yes** *5.3.4.2.3, p4, 64-80*
Indication(s) to be studied: Study 3: Detrusor hyperreflexia due to neurogenic conditions	**Indications Studied:** Study 3: Detrusor hyperreflexia *5.3.4.2.3, p3* [See also entry criteria *5.3.4.2.3, p4*]	**Yes** *5.3.4.2.3, p3, 4, 49-50*
Age group & population in which study will be performed: Study 3: Ages eleven to fifteen years	**Age group & population in which study was performed:** Study 3: 11-15 years, inclusive *5.3.4.2.3, p4*	**Yes** *5.3.4.2.3, p4* , 49
Number of patients to be studied or power of study to be achieved: Study 3: Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.	**Number of patients studied or power achieved:** Study 3: 11. *5.3.4.2.3, p4* 10 pts completed the study (1 patient withdrew consent). Gender breakdown: 5 M, 6 F. *5.3.4.2.3, p6* Age breakdown: 11-13 yrs: N=8; 14-15 yrs: N=3. *5.3.4.2.3, p6* Racial breakdown: 8 white, 3 black. *5.3.4.2.3, p6* A 15 y/o withdrew consent after 63 days (this same pt was unable to give blood for PK studies). *5.3.4.2.3, p49* PK population: 10 (1 unable to have blood drawn) *5.3.4.2.3, p49*	**Yes** *5.3.4.2.3, p6, 49*
Entry criteria: Study 3: Not specified	**Entry criteria used:** Study 3: Male & female 11-15 years of age, inclusive. Stable neurological disease (myelomeningocele, sacral atresia, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia requiring intermittent catheterization for management or urinary drainage. Body weight or BMI within normal range (between the 5^{th}-95^{th} percentiles), according to the CDC Growth and BMI charts for the US *5.3.4.2.3, p4*	**N/A**

Clinical endpoints:	**Clinical endpoints used:**	
Study 3: 1. PK: appropriate analysis of tolterodine & DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group.	**Study 3:** *5.3.4.2.3, p4* 1. PK: Primary: PK parameters for the active moiety, including: area under the **serum** concentration-time curve to 24 hours after dosing (AUC_{0-24}); maximum observed plasma concentration (C_{max}) and minimum observed plasma concentration (C_{min}). Active moiety was defined as the sum of the unbound tolterodine and DD 01 concentrations. Secondary: PK parameters for tolterodine and DD 01, including: AUC_{0-24}, C_{max}, the time of occurrence of C_{max} (t_{max}), C_{min} and apparent terminal half-life ($t_{1/2,z}$). For tolterodine, oral steady-state volume of distribution (V_{ss}/F) and oral clearance (CL/F) were also calculated.	**1. Yes** *5.3.4.2.3, p4, 51-57* Sponsor reports serum, not plasma values; this is acceptable to the Division's Clinical Pharmacologists.
2. PD: appropriate urodynamic evaluation. Evaluations may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions. 3. Dose-response: characterization of dose (in mg/kg)-effect (urodynamic) and concentration-effect (urodynamic) 4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinent episodes per day 5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters	2. Clinical effects: PD variables included: volume to first detrusor contraction of magnitude >10 cm H_2O pressure, functional bladder capacity and leak point pressure, intravesical volume at 20 and 30 cm H_2O pressure, maximal cystometric capacity (intravesical volume at 40 cm H_2O pressure), and bladder compliance (defined as delta volume/delta pressure) all measured at each dose level. Also, tolterodine dose-PD effects were determined by the assessment of urodynamic parameters at each dose level. **Tolterodine/DD 01 (active moiety) concentration-PD effects** were determined by the assessment of urodynamic parameters at the PK dose (4 mg/day). Patient diary (clinical effect) variables included: mean number of catheterizations/micturitions per 24 hours, mean volume per catheterization/micturition and mean number of incontinence episodes per 24 hours, all at each dose level.	**2-4. Yes** *5.3.4.2.3, p4, 58-70* Concentration-effect was described for active moiety only; however, this is acceptable to the Division's Clinical Pharmacologists. **5-6. Yes** *5.3.4.2.3, p4, 70-80*

6. Safety: number of patients terminated prematurely	3. Safety – Hematology and serum chemistry tests, ECGs, GI function assessment and adverse events 4. Health economics – health care utilization data were collected throughout the trial. These data will contribute to an estimate of the direct costs of detrusor hyperreflexia in these patients.	
Timing of assessments: if appropriate Study 3: For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with tolterodine.	**Timing of assessments:** Study 3: Washout of 6-14 days prior to baseline visit. First patient diary completed after at least three days washout, and over three days prior to the baseline visit. Urodynamics, patient diary, safety data (including assessment of GI function, ECGs, clinical laboratory results and AEs and health care utilization data) collected every four weeks, after completion of each dose level. PK data collected following the 4 mg dose level only. *5.3.4.2.3., p3*	**Yes** *5.3.4.2.3, p27*
Drug specific safety concerns: Study 3: Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents	**Drug specific safety concerns evaluated:** Study 3: One patient withdrew consent. One pt had 2 SAEs – erythema, pressure sores. No clinically significant changes in ECG or lab parameters. Constipation most common and only AE considered drug related (in 1 pt at 6 mg). No dry mouth, psychiatric or behavioral abnormalities, 1 abd pain; no dose-AE relationship. *5.3.4.2.3, p7*	**Yes** *5.3.4.2.3, p7, 70-71*
Drug information: Study 3: **Amended August 5, 2002 and October 8, 2003** • **Route of administration:** Oral	**Drug information:** Study 3: *5.3.4.2.3, p4* • **Route of administration:** Oral	**Yes** *5.3.4.2.3, p23-24*

• **Dosage:** Sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 2 mg/day for four weeks, 4 mg /day for four weeks and 6 mg/kg/day for four weeks • **Regimen:** Daily • **Formulation:** Tolterodine extended release capsules (commercially not yet available)	• **Dosage:** Doses 2 mg, 4 mg and 6 mg qD, escalating every 4 weeks • **Regimen:** Daily • **Formulation:** Tolterodine L-tartrate PR capsules, 2 & 4 mg	
Statistical information (statistical analysis of the data to be performed): **<u>Study 3:</u>** 1. PK: descriptive analysis to include reporting of AUC, C_{max}, & C_{min} for tolterodine and DD 01 2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment. 3. Diary: number of micturitions per 24 hours and number of incontinence episodes per day (diary data) to be tabulated as a function of dose (mg/kg).	**Statistical information (statistical analysis of the data performed):** **<u>Study 3:</u>** *5.3.4.2.3, p5* All patients who received study drug were included in the safety analysis. PK variables were summarized using descriptive statistics. Serum concentration profiles were presented graphically. PK variables were compared (informally) with similar variables from PK studies in adults and in children 11-15 years old without neurological compromise. Relationships of interest such as AUC by age, weight and BMI were investigated. Descriptive statistics for clinical effect variables were calculated by dose period, along with descriptive statistics for changes and percentage changes from baseline in these variables. Hodges-Lehman estimates and non-parametric 95% confidence intervals were calculated for these estimates. Volume based urodynamic variable were also calculated as	**1. Yes** *5.3.4.2.3, p6, 54, 55* **2. Yes** *5.3.4.2.3, p6, 58-62* **3. Yes** *5.3.4.2.3, p7, 64-67*

Baseline measurements will be contrasted with on treatment measurements.	values normalized to theoretical bladder capacity (%) and descriptive statistics for these normalized values were presented. The scoring of incontinence was summarized in frequency tables by dose period. Graphic presentations of the dose-effect relationship and the active moiety concentration-effect relationship for the clinical effect variables were evaluated.	
4. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.	Adverse events were coded according to the MedDRA and summarized in frequency tables by dose period. The frequency of laboratory test results that were outside the normal range and the frequency of abnormal ECGs were summarized by dose period. Means were calculated for each ECG variable for each series of measurements at each dose period. The change from baseline was also calculated for each ECG variable by dose period. Frequencies of QT, QTcF and QTcB intervals and changes from baseline in QT, QTcF and QTcB intervals that exceeded defined cut-off points were determined. Plots of changes in QTcF versus serum concentrations of tolterodine and DD 01 and versus AUC_{0-24} for tolterodine and DD 01 were examined for possible relationships. Assessments of GI function were summarized by dose period in frequency tables.	**4. Yes** *5.3.4.2.3, p7, 70-80*
Labeling that may result from the studies: **Study 3:** Appropriate changes to the label to incorporate the study results will be made.	**Did the sponsor submit proposed labeling?** The sponsor proposes to maintain the current approved labeling for Detrol LA capsules, except for the proposed changes as outlined in the following Sections. No labeling changes were submitted for Detrol immediate release tablets. **Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section Pharmacokinetics in special populations – Pediatric subsection *1.2.c, p5-6***	**Yes** However, efficacy is not demonstrated in this study.

The sponsor proposes to delete the following sentence:

"The pharmacokinetics of tolterodine has not been established in pediatric patients."

And replace it with the following five paragraphs and table:

"The pharmacokinetics of tolterodine immediate and extended release were evaluated in pediatric patients ranging in age from 5 to 15 years. Steady-state pharmacokinetic parameters are presented in Table 2.

Table 2. Summary of Mean (±SD) Pharmacokinetic Parameters of Detrol and it Active Metabolite (5-hydroxymethyl metabolite) in Pediatric Patients

	Tolterodine				5-hydroxymethyl metabolite			
	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)
5 – 10 yr † 2 mg bid EM (n=9)	1 (0.5 – 2)	11.5 (6.5)	2.6 (1.4)	2.0 (0.8)	2 (1 – 2)	8.5 (4.0)	2.8 (1.0)	2.6 (1.0)
5 – 10 yr 2 mg qd EM (n=302)	---- ‡	----	1.5 (1.6)	----	----	----	0.89 (0.39)	----
PM (n=20)	----	----	6.9 (3.2)	----	----	----	----	----
11 – 15 yr 4 mg qd EM (n=27)	3 (2 – 7)	3.7 (2.7)	1.8 (1.5)	15 (12)	4 (2-9) ----	2.4 (0.93)	1.3 (0.43)	14 (11)
PM (n=3)	3 (3 – 4)	19 (1.4)	14 (0.83)	29 (11)		----	----	----

	Cmax = Maximum serum concentration; tmax = Time of occurrence of Cmax; Cavg = Average serum concentration; t1/2 = Terminal elimination half-life. * Data presented as median (range). † Dosed using immediate release tablets ‡ not applicable. "At an equivalent daily dose of tolterodine immediate release, C_{avg} and C_{max} of tolterodine and the 5-hydroxymethyl metabolite were higher in children 5 to 10 years of age than in adults, while t_{max} and $t_{1/2}$ were similar between children and adults. "The elimination half-life appeared prolonged in pediatric patients 11 to 15 years of age as compared to the adult population. However, C_{avg}, C_{max} and t_{max} were comparable between the two populations at the 4-mg daily dose. "In patients ranging in age from 1 month to 4 years who received a 0.030 mg/kg twice-daily dose of an investigative tolterodine tartrate oral solution, tolterodine oral clearance (4.9 ± 4.5 L/h/kg) was higher and elimination half-life (1.5 ± 0.6 h) was shorter than values observed in children 5 to 10 years of age (CL/F = 3.7 ± 3.6 L/h/kg; $t_{1/2}$ = 2.2 ± 1.0 h). "Evaluation of the pharmacokinetic/pharmacodynamic relationship in children based on active moiety AUC suggests that administration of a tolterodine daily dose of 2 mg for patients weighing ≤35 kg or 4 mg for patients with body weight >35 kg would provide active moiety exposure that is similar to that in adults receiving 4 mg daily." **Sponsor Proposed Addition of Pediatric Patients Subsection to CLINICAL STUDIES Section** The sponsor proposes to add the following Pediatric Patients Subsection: "DETROL LA 2 mg was evaluated in pediatric patients 5 to 10 years of age with the symptoms or urinary urgency, frequency and urge incontinence in two randomized, multicenter, placebo-controlled, double-blind, 12-week studies.	

	A total of 487 patients received DETROL LA 2 mg in the morning and 224 received placebo. Efficacy in this population has not yet been demonstrated." **Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection** *1.2.c, p11* The sponsor proposes to delete the following sentence: "The safety and effectiveness of tolterodine in pediatric patients has not been established. " And replace it with the following four sentences: "The safety of DETROL LA has been demonstrated in two Phase 3 placebo-controlled, double-blind, 12-week studies of 486 pediatric patients ages 5 to 10. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults. The overall safety profile of tolterodine in this age group was comparable to that seen in adults (see **Clinical Studies** and **Adverse Reactions**)." **Sponsor Proposed Addition of Pediatric Studies Subsection to ADVERSE REACTIONS Section** ***1.2.c, p13-14*** The sponsor proposes to add the following Pediatric Studies Subsection: "In two placebo-controlled clinical trials of DETROL LA Capsules, 710 pediatric patients ages 5 to 10 years were treated with DETROL LA (n=486) or placebo (n=224). Patients were treated with DETROL LA 2 mg for 12 weeks. The overall frequency of adverse experiences was almost identical in the DETROL LA and placebo treatment groups (48% and 49%, respectively). Urinary tract infection was the most common adverse event occurring at a rate greater than placebo reported by pediatric patients receiving DETROL LA. Dry mouth was only reported in 0.8% of patients treated with DETROL LA and in 1.8% of patients receiving placebo. A serious adverse event was	

reported by 1% (n=6) of pediatric patients receiving DETROL LA and 1% (n=2) of patients receiving placebo.

"The frequency of discontinuation due to adverse events was 3% for both the DETROL LA and placebo treatment groups. Table 5 lists the adverse events reported in 1% or more of pediatric patients treated with DETROL LA 2 mg once daily in the 12-week studies."

Table 5. Incidence* (%) Of Adverse Events Exceeding Placebo Rate And Reported In ≥1% Of Pediatric Patients Treated With DETROL LA (2 mg once daily) in Two 12-Week, Phase 3 Clinical Trials

Body System	Adverse Event	%DETROL LA (n=486)	%Placebo (n=224)
Gastrointestinal disorders	Abdominal pain	5	3
	Vomiting	4	2
	Diarrhea	3	1
	Constipation	2	1
Infections and infestations	Urinary tract infection	7	4
	Ear infection	1	0
Psychiatric disorders	Abnormal behavior	2	0
Respiratory, thoracic, and mediastinal disorders	Rhinitis	2	0

*in nearest integer.

Sponsor Proposed Changes to Revision date

The sponsor proposes to change the revision date listed at the very end of the physician insert from:

"Revised July 2003

818 229 006"

To:

"Revised Month Year"

Format of reports to be submitted: A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guidelines for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports submitted:** Final study report format was acceptable.	**Yes**
Timeframe for submitting reports of the studies: Amended March 3, 2003 On or before October 15, 2003	**Date study reports were submitted:** October 14, 2003	**Yes**
Additional information:	**Conclusions:** *5.3.4.2.3, p 8* **Study 3:** Drug exposure, as measured by AUC and C_{max} of the active moiety, similar to that previously observed in 11-15 year olds w/OAB and in adults. No apparent concentration-effect relationship. A dose-effect relationship was not observed for urodynamic and micturition diary data parameters. Specifically, improvement from baseline was seen in: • Functional bladder capacity, only at the 4 mg dose, • Mean number of incontinence episodes per 24 hours, at all doses, but without a dose-effect relationship and • Mean volume per catheterization/micturition, only at the 4 mg dose. 95% confidence limits on change from baseline at each dose included 0 for:	**N/A**

	• Volume to first detrusor contraction, • Intravesical volume at 20 cm H_2O and • Mean number of catheterizations/micturitions per 24 hours. Generally well tolerated, no new safety concerns identified.	

ATTACHMENT D

Study 4 Pediatric Exclusivity Determination Template

Written Request Item – January 23, 2001	Information Submitted	Condition Met
Types of Studies/Study Design: Study 4: Clinical efficacy, PK and safety study in patients with overactive bladder Study design: Minimum 12-week, double-blind, two parallel group, placebo controlled, two-to-one (test drug/placebo) randomized, clinical efficacy and safety study followed by a minimum 12-week safety extension study Objectives: 1. To compare the clinical efficacy (as assessed by the number of incontinence episodes) of tolterodine extended release and placebo. 2. To document the safety and tolerability of tolterodine extended release capsules in pediatric patients with overactive bladder. 3. To evaluate the population PK of tolterodine and its metabolite (DD01) following administration of tolterodine extended release capsules using sparse sampling technique. 4. To evaluate dose-effect (diary data) and concentration-effect (diary-data) in order to establish one or more safe and effective dosage regimens in pediatric patients with overactive bladder.	**Types of Studies:** Study 4: 583E-URO-0084-020 Phase III randomized, double-blind, placebo-controlled (2:1 ratio) multinational clinical efficacy and safety study. *5.3.5.1.1, p4* Duration of treatment 12 weeks. *5.3.5.1.1, p5* Objectives: *5.3.5.1.1, p4* Primary: To compare the clinical efficacy of tolterodine PR 2 mg q.d. and placebo, as defined by the change in total number of incontinence episodes/week after 12 weeks of treatment, in children 5 to 10 years of age. Secondary: To compare the clinical efficacy, as measured by other micturition chart and rating scale variables, and safety of tolterodine PR 2 mg qd. and placebo after 12 weeks of treatment. DETAPE-0581-008 Phase III randomized, double-blind, placebo-controlled (2:1 ratio) multinational clinical efficacy and safety study. *5.3.5.1.4, p3* Duration of treatment 12 weeks. *5.3.5.1.4, p4* Objectives: *5.3.5.1.4, p3* Primary: To compare the clinical efficacy of tolterodine PR 2 mg qd. and placebo regarding the change in number of daytime incontinence episodes/week after 12weeks of treatment in children 5 to 10 years of	**Design: Yes** 020: *5.3.5.1.1, p4, 26-7* 008: *5.3.5.1.4, Appendix 1.9* 021: This extension study was an open label safety and efficacy extension study, comprising pts from studies 020 (271 of the original 342) and 018 (27 of the original 31) *5.3.5.1.3, p3, 20, 27* **Objectives:** **1. Yes** 020: *5.3.5.1.1, p20* 008: *5.3.5.1.4, p19*

	age with symptoms of urge urinary incontinence, suggestive of detrusor instability. Secondary: To compare the clinical efficacy of tolterodine PR 2 mg qd. and placebo regarding change in: • number of daytime incontinence episodes/week (after 4 weeks of treatment) • Mean number of micturitions per 24 hours • Mean urinary volume voided per micturition • Number of nights with nocturnal enuresis per week • Parent/guardian-reported quality of life • Parent/guardian-reported treatment satisfaction To compare tolterodine PR 2 mg qd and placebo with regard to safety and tolerability The population PK/PD objectives were to • Estimate each patient's exposure to both tolterodine and its active metabolite, DD 01 • Explore the exposure-response relationship of tolterodine, DD 01 and the combined exposure (active moiety) graphically • Develop a statistical model describing the exposure-response relationship of the combined exposure from tolterodine and DD 01 • Evaluate the influence of various patient demographic factors and covariates on the PD of tolterodine • Explore the relationship between exposure and safety of tolterodine defined by incidence of AEs **583E-URO-0084-021** Phase III multicenter, **open-label** long-term safety, tolerability and clinical efficacy extension study following 020 or 018 *5.3.5.1.3, p3* Duration of treatment 12 months *5.3.5.1.3, p3*	**2. Yes** **020:** *5.3.5.1.1, p20-21* **008:** *5.3.5.1.4, p20* **021:** *5.3.5.1.3, p19* **3. Yes** PK data is pooled from studies 018, 014 (rich sampling) and 008 and 020 (sparse sampling) **020 & 008:** *5.3.3.5.2, p22* **008:** *5.3.5.1.4, p20* **4. Yes** **020 & 008:** Pooled data (008 & 020) on concentration-effect *5.3.3.5.2, p73-75*

	Objectives: *5.3.5.1.3, p3* Primary: To study the safety and tolerability of tolterodine PR capsules during 12 months of treatment in children 5-15 years of age Secondary: To document long-term clinical efficacy and to perform other safety assessments.	"Dose-effect" data is based on mg/kg dose; however, only one dose was evaluated in each study. *5.3.5.1.1.1 and 5.3.5.1.4.1*
Indication(s) to be studied: **Study 4:** Overactive bladder	**Indications Studied:** **Study 4:** **020, 008 and 021**: Symptoms of urinary urge incontinence suggestive of detrusor instability *5.3.5.1.1, p4* and *5.3.5.1.4, p3* [See also entry criteria *5.3.5.1.1, p5* , *5.3.5.1.4, p4 and 5.3.5.1.3, p3*]	**Yes** **020:** *5.3.5.1.1, p27-8* **008:** (this study had an additional entry criterion of >=6 micturitions/day) *5.3.5.1.4, p28* **021:** 2 different criteria used (study 020 v. 018) – 018 required urgency AND >= 8 micturitions/24 hours AND/OR >= one incontinence episode/week *5.3.5.1.3, p24-26*

Age group & population in which study will be performed: **Study 4:** Ages five to ten years	**Age group & population in which study was performed:** **Study 4:** **020 and 008:** >=5 and <= 10 years of age. *5.3.5.1.1, p5* and *5.3.5.1.4, p4* **021:** **5-15 years** of age *5.3.5.1.3, p3* [5-10 years from study 020; **11-15** years from study 018]	Yes **020:** *5.3.5.1.1, p27* **008:** *5.3.5.1.4, p28* **021:** The pts originally from study 018 were 11-15 years (N=27 of 298) *5.3.5.1.3, p25*
Number of patients to be studied or power of study to be achieved: **Study 4: Amended November 15, 2001** Enroll approximately 300 patients, with approximately equal number of patients in the five-seven year old age group and in the eight-ten year old age group, to ensure a minimum of 100 patients completing 24 weeks of treatment with tolterodine tartrate extended release capsules.	**Number of patients studied or power achieved:** **Study 4:** **020:** ITT/Safety population: N=342 (235 randomized to tolterodine PR, 107 randomized to placebo) *5.3.5.1.1, p4* • Age distribution: 5-7 years: N= 178 (55 placebo, 123 tolterodine); 8-10 years: N= 164 (52 placebo, 112 tolterodine). [Calculated from *5.3.5.1.1, Appendix 18*] • **Two 4 y/o's and one 11 y/o included in placebo gp.** *5.3.5.1.1, Appendix 18* Per protocol population: N= 302 (212 tolterodine, 90 placebo) *5.3.5.1.1, p6* PK analysis (pooled): 102 randomized to tolterodine PR (133 excluded due to not meeting 008's inclusion criteria or missing data) *5.3.3.5.2, p26, Appendix 7-10* PD analysis (pooled): 157 pts (183 excluded due to not meeting 008's inclusion criteria or missing data *5.3.3.5.2, p29* Gender breakdown: 186 M (127 tolterodine, 59 placebo), 156 F (108	Yes **020:** 020 Placebo group had 3 Ss outside age ranges *5.3.5.1.1, p4, 6, 50, 53* **008:** *5.3.5.1.4, p4, 6, 52, 74 & 5.3.3.5.2, p26* **021:** *5.3.5.1.3, pp 3, 5, 41-43, 46-7*

	tolterodine, 48 placebo) *5.3.5.1.1, p 55* Racial breakdown: 318 White (218 tolterodine, 100 placebo), 20 Asian/Pacific Islander (13 tolterodine, 7 placebo), 4 mixed race (all tolterodine) *5.3.5.1.1, p 55* **008:** ITT population: N= 369 (252 randomized to tolterodine PR, 117 randomized to placebo) *5.3.5.1.4, p4* Safety population: N=368 [251 randomized to tolterodine PR (1 pt did not take a single dose *5.3.5.1.4, p51)*, 117 randomized to placebo] *5.3.5.1.4, p4* Population PK/PD population: N= 337 [220 randomized to tolterodine PR (exclusions for missing data), 117 randomized to placebo] *5.3.5.1.4, p4, 74 & 5.3.3.5.2, p26* Completer population: N=343 (234 tolterodine, 109 placebo) *5.3.5.1.4, p6* Gender breakdown: 193 M (128 tolterodine, 65 placebo), 176 F (124 tolterodine, 52 placebo) *5.3.5.1.4, p 57* Racial breakdown: 333 White (225 tolterodine, 108 placebo), 8 Black (7 tolterodine, 1 placebo), 21 Asian (16 tolterodine, 5 placebo), 7 unspecified (4 tolterodine, 3 placebo) *5.3.5.1.4, p 57* **021:** ITT/safety population: N=298 [271 from 020 and 27 from 018 (7 on 2 mg, 20 on 4mg)]. Completer population: N=170 (154 from 020, 16 from 018) *5.3.5.1.3, p3* and *p5* Gender breakdown (from Study 020): 155 M, 116 F *5.3.5.1.3, p48* Racial breakdown (from Study 020): 251 White, 17 Asian/Pacific Islander, 3 mixed race *5.3.5.1.3, p48* 254 pts from study 020 completed at least 24 weeks of treatment *2.7.4, p16* 154 pts from study 020 completed 12 months *5.3.5.1.3, pp 3, 5*	

Entry criteria: **Study 4:** Not specified	**Entry criteria used:** **Study 4:** **020:** Male or female >=5 and <=10 years of age. >=1 incontinence or dampness episode per day during waking hours for at least 5 out of 7 days (confirmed by micturition chart during run-in period). *5.3.5.1.1, p 5* **008:** Male or female aged 5 to 10 years inclusive; patients with symptoms of urge urinary incontinence defined as >= 1 incontinence episode per day (i.e., during waking hours) for at least 5 out of 7 days, suggestive of detrusor instability, as confirmed by micturition diary during run-in period; patients with a mean urinary frequency of >=6 micturitions/24 hours as confirmed by micturition diary during run-in period *5.3.5.1.4, p 4* **021:** Children with symptoms of urinary urge incontinence suggestive of detrusor instability appropriately included in and having completed Study 018 or 020. Age 5-10 years (Study 020) or 11-15 years (Study 018) *5.3.5.1.3, p3*	**N/A**
Clinical endpoints: **Study 4:** 1. *Primary endpoint:* change from baseline in number of incontinence episodes per week after 12 weeks of treatment. *Other endpoints:* the change from baseline in mean number of micturitions per 24 hours after 12 weeks of treatment, the change from baseline in mean urinary volume voided per micturition after 12 weeks of treatment, and appropriate population pharmacokinetic analysis of	**Clinical endpoints used:** **Study 4:** *5.3.5.1.1., p5* **020:** 1. Efficacy: Primary: Change from baseline in total number of incontinence episodes/week (during waking hours) after 12 weeks of treatment Secondary: Changes from baseline in mean number of micturitions/24 hr, mean volume voided/micturition, number of "gross" incontinence episodes/week, and VASC results, and parent's assessment of treatment benefit.	**1. Yes** **020:** *5.3.5.1.1, p39-42* **008:** *5.3.5.1.4, p20-21* **021:** No PK analysis *5.3.5.1.3, p29-31*

tolterodine and DD 01 metabolite data. 2. Dose-response: characterization of dose (in mg/kg)-effect (diary data) and concentration-effect (diary data). 3. Safety: incidence and severity of adverse events, postvoid residual urine, cardiovascular (including electrocardiograms) and laboratory abnormalities. 4. Safety: number of patients terminated prematurely from the trial	2. Safety: Measurement of PVR urine volume, ECG recordings, laboratory safety values, and reporting of adverse events (AEs). **008:** *5.3.5.1.4, p5* Primary: Change from baseline in total number of daytime incontinence episodes/week after 12 weeks of treatment Secondary: Efficacy - Changes from baseline in • number of daytime incontinence episodes/week after 4 weeks of treatment • mean number of micturitions/24 hr after 4 and 12 weeks of treatment • mean volume voided/micturition after 4 and 12 weeks of treatment • number of nights with nocturnal enuresis episodes per week after 4 and 12 weeks of treatment Parent/guardian-reported outcomes: Change from baseline in PEMQoL after 12 weeks of treatment, parent/guardian-reported treatment satisfaction at Week 12 Population PK/PD: PK parameters, exposure-response, and exposure-safety relationship for tolterodine PR, its major metabolite (DD 01) and the active moiety (the sum of unbound serum concentrations of tolterodine and DD 01) Pharmacogenomics:	**2. Yes** "Dose-effect" data is based on mg/kg dose; however, only one dose was evaluated in each study. *5.3.5.1.1.1 and 5.3.5.1.4.1* **020 & 008:** *5.3.3.5.2, pp24-5* **021:** Data were analyzed separately by study of origin and dose (for study 018 pts). *5.3.5.1.3, p19* **3. Yes** **020:** *5.3.5.1.1, p42* **008:** AE reporting and PVR measurement only *5.3.5.1.4, p21, 28* **020 & 008:** *5.3.3.5.2, pp25, 55*

	Relationship between cytochrome P450 genotype, phenotype and PK parameters. Results of further genetic testing of samples collected in this study will be reported separately Safety and tolerability: Incidence and severity of AEs, incidence of increased PVR, number of and reasons for withdrawal from the study **021:** Primary: incidence, duration and intensity of AEs during the 12-month treatment period Secondary: • Change in baseline in number of incontinence episodes/week at study end • Change in baseline in mean # of micturitions/24 hr at study end • Change in baseline in mean urinary volume voided at study end • Incidence of increased PVR urine, as measured by ultrasonography/bladder scan • Number of and reasons for withdrawal • Change in baseline in clinical chemistry and hematology • Change in baseline in the Visual Analog Scale for Children 9 years and older (020) • Treatment benefit at study end	**021:** No ECG data *5.3.5.1.3, p31,35-6* **4. Yes** **020:** *5.3.5.1.1, 53-6* **008:** *5.3.5.1.4, p21* **021:** *5.3.5.1.3, p42-3, 100*
Timing of assessments: if appropriate **Study 4:** Not specified	**Timing of assessments:** **Study 4:** **020:** 7-day micturition chart recordings during run-in (before randomization) and during the last week of treatment (week 12)	**N/A**

	5.3.5.1.1., p4, 27 **008:** 7-day micturition chart recordings during run-in (before randomization), during the 3rd week of treatment and during the last week of treatment (week 12) 5.3.5.1.4., *p4*	
Drug specific safety concerns: **Study 4:** Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents (e.g., constipation, dry mouth)	**Drug specific safety concerns evaluated:** **Study 4:** **020:** Adverse events, clinical laboratory tests, ECGs and post-void residual (PVR) urine volume included as safety assessments. *5.3.5.1.1., p4* Withdrawal due to AE identical (4.7%) in each group. 4 tx, 2 placebo SAEs – tx SAEs not related. No clinically significant changes in ECG or lab parameters in either group. Abd pain, pyrexia, diarrhea, UTI and psychiatric disorders (mood alterations/disturbances) more frequent in tx group. *5.3.5.1.1, p8* **008:** Adverse events, post-void residual urine volume (PVR) and vital signs evaluations included as safety assessments. *5.3.5.1.4, p4* Few SAEs or withdrawals due to AEs. UTI twice as frequent in tolterodine group, only one judged related. Higher rates of nervous system AEs (primarily headaches) but lower rates of psychiatric disorders. *5.3.5.1.4, p7* **021:** Adverse events, clinical laboratory tests, and post-void residual urine volume (PVR) included as safety assessments. *5.3.5.1.3, p3* 8 serious AEs in 020, none considered related. 3% withdrew due to nonserious AEs. 3 pts with mood/behavior alterations; 6 w/increased PVR to >20% theoretical capacity. *5.3.5.1.3, p5*	**Yes** GI function not explicitly elicited, although GI AEs reported *2.7.4, p12* **020:** *5.3.5.1.1., p4, 25-6, 88-100* **008:** *5.3.5.1.4, p4, 7, 20, 84-117* **021:** *5.3.5.1.3, p3, 5, 63-81*

Drug information: **Study 4:** • **Route of administration:** Oral • **Dosage:** 2 mg • **Regimen:** Once a day in the morning • **Formulation:** Tolterodine extended release capsules	**Drug information:** **Study 4: 020 and 008:** *5.3.5.1.1, p5* and *5.3.5.1.4, p4* • **Route of administration:** Oral • **Dosage:** 2 mg • **Regimen:** Once daily • **Formulation:** Tolterodine L-tartrate prolonged release (PR) capsules **021:** *5.3.5.1.3, p3* • **Route of administration:** Oral • **Dosage:** 2 mg or 4 mg • **Regimen:** Once daily • **Formulation:** Tolterodine L-tartrate prolonged release (PR) capsules	**Yes** **020 & 008:** If the pt were unable to swallow capsule, s/he was allowed to open the capsule & sprinkle beads on food. While bioequivalence of opened and intact capsules has not been demonstrated, the mode of administration was not specified in the Written Request *5.3.5.1.1, pp 31 and 5.3.5.1.4, pp31* **020:** *5.3.5.1.1, pp 30-1* **008:** *5.3.5.1.4, pp30-1* **021:** Placebo pts from study 020 were given 2 mg PR po qD. The pts from study

		018 received their original dose, either 2 or 4 mg PR po qD *5.3.5.1.3, p26-7*
Statistical information (statistical analysis of the data to be performed): **<u>Study 4:</u>** 1. All statistical tests will be two-sided and the level of significance will be 0.05. 2. PK: appropriate population PK analysis for drug and DD 01 metabolite. 3. Micturition Diary Data: diary data are to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment. 4. Safety: safety measurements are to be tabulated by treatment group, body system and preferred term for both 12 week efficacy and 12 week safety extension trials. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data. Patients with abnormal postvoid residual urine findings, serious adverse events, or who withdraw due to an adverse event will be reported on a case-by-case basis.	**Statistical information (statistical analysis of the data performed):** **<u>Study 4:</u>** **<u>020:</u>** *5.3.5.1.1., p5* Primary analysis based on ITT population (all randomized subjects who received at least 1 dose of study medication). Missing micturition chart data were replaced using the last observation carried forward (LOCF) technique. ANOVA of change from baseline in total number of incontinence episodes/wk, with treatment group comparisons and 85% confidence intervals based on least squares means from the ANOVA model. Similar ANOVA models for changes from baseline in mean number of micturitions /24 hrs, mean volume voided/micturition, and number of "gross" incontinence episodes/week. Parent's assessment of treatment benefit compared between the two treatment groups using Wilcoxon rank-sum test. Descriptive statistics for VASC results (no formal statistical comparison due to small expected numbers of subjects 9 years of age and older). Proportions of withdrawals and proportions of withdrawals due to AEs compared using chi-square tests. Proportions of subjects with positive PVR urine volume (defined as >+20% of the theoretical	**1. Yes** **<u>020:</u>** *5.3.5.1.1., p47* **<u>008:</u>** *5.3.5.1.4, Appendix 1.9, p3* **2. Yes** PK data are pooled from studies 018, 014 (rich sampling) and 008 and 020 (sparse sampling) **<u>020 & 008:</u>** *5.3.3.5.2, p22* **3. Yes** **<u>020 & 008:</u>** "Dose-effect" data is based on mg/kg dose; however, only one dose was evaluated in each study.

	bladder capacity [30 + 30(age)ml]) compared using a chi-square test. Incidence rates for all treatment emergent AEs calculated by treatment group. Descriptive statistics for ECGs and laboratory data, and frequencies of abnormal results and shifts in results were calculated. **008:** *5.3.5.1.4., p5* Efficacy and Safety: Primary analysis based on ITT population (all randomized subjects) Missing micturition diary data were replaced using the last observation carried forward (LOCF) technique. ANCOVA with number of daytime incontinence episodes/week at baseline included as covariate, and treatment, country and treatment-by-country interaction as factors (latter excluded if p>0.1). Similar ANCOVA models were applied for changes from baseline to Weeks 4 and 12 in mean number of micturitions /24 hrs, mean volume voided/micturition, and number of nights with nocturnal enuresis episodes per week. Degree of improvement in continence after 12 weeks of treatment was compared between the two treatment groups using the Wilcoxon rank sum test, and the difference in proportion of continent patients was tested with the Chi-square test. Parent/guardian assessment of treatment satisfaction was compared between the two treatment groups using a Student's t-test. Changes from baseline in PEMQoL scales after 12 weeks of treatment were compared between treatment groups using Student's t-tests. Post-void residual urine volume and vital signs were summarized by treatment group and visit. The incidence of AEs was calculated for each treatment group. Population PK/PD: Population PK methods were used to obtain individual PK parameters estimates. Simulated steady-state concentration-time profiles for tolterodine, DD 01 and the active moi8ety were generated for each patient and the AUC_{0-24} was	*5.3.5.1.1.1 and 5.3.5.1.4.1* **021:** Data were analyzed separately by study of origin and dose (for study 018 pts). *5.3.5.1.3, p19* **4. Yes** **020:** *5.3.5.1.1., p50, 89-93* **008:** *5.3.5.1.4, pp84-117* **021:** *5.3.5.1.3, p63-92*

	calculated using the trapezoidal rule. The relationship between the primary efficacy measure and exposure to tolterodine was explored graphically. The CART procedure was used to determine breakpoints in activity moiety AUC_{0-24} by efficacy outcome. The Kruskal-Wallis test was used to detect statistically significant differences in efficacy outcome by the activity moiety AUC_{0-24} breakpoint. Regression analyses were then used to investigate whether exposure (the activity moiety AUC_{0-24} and the breakpoint) and/or selected demographic characteristics were statistically significant predictors of patient outcome (end-pf-treatment change from baseline). A forward selection method with a level of significance of 0.05 was used. **021:** *5.3.5.1.3, p4* Analyzed in descriptive manner, as no control group. Visit 1 (018) or Visit 2 (020) was defined as baseline for micturition chart variables and VASC. The three groups (020 pts on 2 mg, 018 pts on 4 mg and 018 pts on 4 mg) are presented separately.	
Labeling that may result from the studies: Appropriate changes to the label to incorporate the study results will be made.	**Did the sponsor submit proposed labeling?** The sponsor proposes to maintain the current approved labeling for Detrol LA capsules, except for the proposed changes as outlined in the following Sections. No labeling changes were submitted for Detrol immediate release tablets. **Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section Pharmacokinetics in special populations – Pediatric subsection *1.2.c, p5-6*** The sponsor proposes to delete the following sentence: "The pharmacokinetics of tolterodine has not been established in pediatric patients." And replace it with the following five paragraphs and table:	**020, 008 & 021:** **Yes** However, efficacy was not demonstrated in either randomized controlled study.

"The pharmacokinetics of tolterodine immediate and extended release were evaluated in pediatric patients ranging in age from 5 to 15 years. Steady-state pharmacokinetic parameters are presented in Table 2.

Table 2. Summary of Mean (±SD) Pharmacokinetic Parameters of Detrol and it Active Metabolite (5-hydroxymethyl metabolite) in Pediatric Patients

	Tolterodine				5-hydroxymethyl metabolite			
	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)
5 – 10 yr † 2 mg bid EM (n=9)	1 (0.5 – 2)	11.5 (6.5)	2.6 (1.4)	2.0 (0.8)	2 (1 – 2)	8.5 (4.0)	2.8 (1.0)	2.6 (1.0)
5 – 10 yr 2 mg qd EM (n=302)	---- ‡	----	1.5 (1.6)	----	----	----	0.89 (0.39)	----
PM (n=20)	----	----	6.9 (3.2)	----	----	----	----	----
11 – 15 yr 4 mg qd EM (n=27)	3 (2 – 7)	3.7 (2.7)	1.8 (1.5)	15 (12)	4 (2-9)	2.4 (0.93)	1.3 (0.43)	14 (11)
PM (n=3)	3 (3 – 4)	19 (1.4)	14 (0.83)	29 (11)	----	----	----	----

Cmax = Maximum serum concentration; **tmax** = Time of occurrence of **Cmax**; **Cavg** = Average serum concentration; **t1/2** = Terminal elimination half-life.

* Data presented as median (range).

† Dosed using immediate release tablets

‡ not applicable.

	"At an equivalent daily dose of tolterodine immediate release, C_{avg} and C_{max} of tolterodine and the 5-hydroxymethyl metabolite were higher in children 5 to 10 years of age than in adults, while t_{max} and $t_{1/2}$ were similar between children and adults. "The elimination half-life appeared prolonged in pediatric patients 11 to 15 years of age as compared to the adult population. However, C_{avg}, C_{max} and t_{max} were comparable between the two populations at the 4-mg daily dose. "In patients ranging in age from 1 month to 4 years who received a 0.030 mg/kg twice-daily dose of an investigative tolterodine tartrate oral solution, tolterodine oral clearance (4.9 ± 4.5 L/h/kg) was higher and elimination half-life (1.5 ± 0.6 h) was shorter than values observed in children 5 to 10 years of age (CL/F = 3.7 ± 3.6 L/h/kg; $t_{1/2}$ = 2.2 ± 1.0 h). "Evaluation of the pharmacokinetic/pharmacodynamic relationship in children based on active moiety AUC suggests that administration of a tolterodine daily dose of 2 mg for patients weighing ≤35 kg or 4 mg for patients with body weight >35 kg would provide active moiety exposure that is similar to that in adults receiving 4 mg daily." **Sponsor Proposed Addition of Pediatric Patients Subsection to CLINICAL STUDIES Section** The sponsor proposes to add the following Pediatric Patients Subsection: "DETROL LA 2 mg was evaluated in pediatric patients 5 to 10 years of age with the symptoms or urinary urgency, frequency and urge incontinence in two randomized, multicenter, placebo-controlled, double-blind, 12-week studies. A total of 487 patients received DETROL LA 2 mg in the morning and 224 received placebo. Efficacy in this population has not yet been demonstrated." **Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection** *1.2.c, p11*	

	The sponsor proposes to delete the following sentence: "The safety and effectiveness of tolterodine in pediatric patients has not been established. " And replace it with the following four sentences: "The safety of DETROL LA has been demonstrated in two Phase 3 placebo-controlled, double-blind, 12-week studies of 486 pediatric patients ages 5 to 10. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults. The overall safety profile of tolterodine in this age group was comparable to that seen in adults (see **Clinical Studies** and **Adverse Reactions**)." **Sponsor Proposed Addition of Pediatric Studies Subsection to ADVERSE REACTIONS Section *1.2.c, p13-14*** The sponsor proposes to add the following Pediatric Studies Subsection: "In two placebo-controlled clinical trials of DETROL LA Capsules, 710 pediatric patients ages 5 to 10 years were treated with DETROL LA (n=486) or placebo (n=224). Patients were treated with DETROL LA 2 mg for 12 weeks. The overall frequency of adverse experiences was almost identical in the DETROL LA and placebo treatment groups (48% and 49%, respectively). Urinary tract infection was the most common adverse event occurring at a rate greater than placebo reported by pediatric patients receiving DETROL LA. Dry mouth was only reported in 0.8% of patients treated with DETROL LA and in 1.8% of patients receiving placebo. A serious adverse event was reported by 1% (n=6) of pediatric patients receiving DETROL LA and 1% (n=2) of patients receiving placebo. "The frequency of discontinuation due to adverse events was 3% for both the DETROL LA and placebo treatment groups. Table 5 lists the adverse events reported in 1% or more of pediatric patients treated with DETROL LA 2 mg	

	once daily in the 12-week studies." **Table 5. Incidence* (%) Of Adverse Events Exceeding Placebo Rate And Reported In ≥1% Of Pediatric Patients Treated With DETROL LA (2 mg once daily) in Two 12-Week, Phase 3 Clinical Trials** *in nearest integer. **Sponsor Proposed Changes to Revision date** The sponsor proposes to change the revision date listed at the very end of the physician insert from: "Revised July 2003 818 229 006" To: "Revised Month Year"	

Body System	Adverse Event	%DETROL LA (n=486)	%Placebo (n=224)
Gastrointestinal disorders	Abdominal pain	5	3
	Vomiting	4	2
	Diarrhea	3	1
	Constipation	2	1
Infections and infestations	Urinary tract infection	7	4
	Ear infection	1	0
Psychiatric disorders	Abnormal behavior	2	0
Respiratory, thoracic, and mediastinal disorders	Rhinitis	2	0

Format of reports to be submitted: A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guidelines for structure and content of clinical study	**Format of reports submitted:** The final study report format is acceptable.	**Yes**

report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.		
Timeframe for submitting reports of the studies: Amended March 3, 2003 On or before October 15, 2003	**Date study reports were submitted:** October 14, 2003	**Yes**
Additional information:	**Conclusions:** **Study 4:** **020:** Efficacy not statistically significant, suggest that appropriate target population is those w/pathological urinary frequency (>7 micturitions/day). Well tolerated, no safety concerns. *5.3.5.1.1, pp6-8* **008:** Efficacy not statistically significant for primary efficacy variable. Statistically significant change from baseline-week 12 in mean volume voided/micturition, in favor of tolterodine. Other secondary efficacy variables non-significant. Three parent/guardian-reported treatment satisfaction measures significant in favor of tolterodine (overall quality of life, change in symptoms and satisfaction with outcomes). PK analysis showed only predictors of response were baseline number of weekly incontinence episodes and level of exposure to active moiety, with >20% of subjects failing to reach the threshold $AUC_{0\text{-}24}$ identified (>=14.4 nM*hr) as that associated with significantly greater response. No exposure-safety relationship w/tolterodine. Well-tolerated, no serious safety concerns. *5.3.5.1.4, pp6-7* **021:** 43% from 020 prematurely withdrawn, most frequently due to lack of efficacy or improvement. 41% from 018 prematurely withdrawn, most frequently due to consent withdrawal. Improvements in micturition chart variables sustained at 6 and 12 mos of treatment in both total group and subgroup with baseline >6 micturitions/day. No safety concerns.	**N/A**

ATTACHMENT E

Critical Analysis Pediatric Exclusivity Determination Template

Written Request Item – January 23, 2001	Information Submitted	Condition Met
Labeling that may result from the studies: Appropriate changes to the label to incorporate the study results will be made.	**Did the sponsor submit proposed labeling?** The sponsor proposes to maintain the current approved labeling for Detrol LA capsules, except for the proposed changes as outlined in the following Sections. No labeling changes were submitted for Detrol immediate release tablets. **Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section Pharmacokinetics in special populations – Pediatric subsection *1.2.c, p5-6*** The sponsor proposes to delete the following sentence: "The pharmacokinetics of tolterodine has not been established in pediatric patients." And replace it with the following five paragraphs and table: "The pharmacokinetics of tolterodine immediate and extended release were evaluated in pediatric patients ranging in age from 5 to 15 years. Steady-state pharmacokinetic parameters are presented in Table 2.	**Yes** However, efficacy was not demonstrated in two randomized, controlled studies.

Table 2. Summary of Mean (±SD) Pharmacokinetic Parameters of Detrol and it Active Metabolite (5-hydroxymethyl metabolite) in Pediatric Patients

	Tolterodine				5-hydroxymethyl metabolite			
	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)	tmax* (h)	Cmax (µg/L)	Cavg (µg/L)	t1/2 (h)
5 – 10 yr † 2 mg bid EM (n=9)	1 (0.5 – 2)	11.5 (6.5)	2.6 (1.4)	2.0 (0.8)	2 (1 – 2)	8.5 (4.0)	2.8 (1.0)	2.6 (1.0)
5 – 10 yr 2 mg qd EM (n=302)	---- ‡	----	1.5 (1.6)	----	----	----	0.89 (0.39)	----
PM (n=20)	----	----	6.9 (3.2)	----	----	----	----	----
11 – 15 yr 4 mg qd EM (n=27)	3 (2 – 7)	3.7 (2.7)	1.8 (1.5)	15 (12)	4 (2-9)	2.4 (0.93)	1.3 (0.43)	14 (11)
PM (n=3)	3 (3 – 4)	19 (1.4)	14 (0.83)	29 (11)	----	----	----	----

Cmax = Maximum serum concentration; **tmax** = Time of occurrence of **Cmax**; **Cavg** = Average serum concentration; **t1/2** = Terminal elimination half-life.

* Data presented as median (range).

† Dosed using immediate release tablets

‡ not applicable.

"At an equivalent daily dose of tolterodine immediate release, C_{avg} and C_{max} of tolterodine and the 5-hydroxymethyl metabolite were higher in children 5

	to 10 years of age than in adults, while t_{max} and $t_{1/2}$ were similar between children and adults. "The elimination half-life appeared prolonged in pediatric patients 11 to 15 years of age as compared to the adult population. However, C_{avg}, C_{max} and t_{max} were comparable between the two populations at the 4-mg daily dose. "In patients ranging in age from 1 month to 4 years who received a 0.030 mg/kg twice-daily dose of an investigative tolterodine tartrate oral solution, tolterodine oral clearance (4.9 ± 4.5 L/h/kg) was higher and elimination half-life (1.5 ± 0.6 h) was shorter than values observed in children 5 to 10 years of age (CL/F = 3.7 ± 3.6 L/h/kg; $t_{1/2}$ = 2.2 ± 1.0 h). "Evaluation of the pharmacokinetic/pharmacodynamic relationship in children based on active moiety AUC suggests that administration of a tolterodine daily dose of 2 mg for patients weighing ≤35 kg or 4 mg for patients with body weight >35 kg would provide active moiety exposure that is similar to that in adults receiving 4 mg daily." **Sponsor Proposed Addition of Pediatric Patients Subsection to CLINICAL STUDIES Section** The sponsor proposes to add the following Pediatric Patients Subsection: "DETROL LA 2 mg was evaluated in pediatric patients 5 to 10 years of age with the symptoms or urinary urgency, frequency and urge incontinence in two randomized, multicenter, placebo-controlled, double-blind, 12-week studies. A total of 487 patients received DETROL LA 2 mg in the morning and 224 received placebo. Efficacy in this population has not yet been demonstrated." **Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection** *1.2.c, p11* The sponsor proposes to delete the following sentence: "The safety and effectiveness of tolterodine in pediatric patients has not	

	been established. " And replace it with the following four sentences: "The safety of DETROL LA has been demonstrated in two Phase 3 placebo-controlled, double-blind, 12-week studies of 486 pediatric patients ages 5 to 10. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults. The overall safety profile of tolterodine in this age group was comparable to that seen in adults (see **Clinical Studies** and **Adverse Reactions**)." **Sponsor Proposed Addition of Pediatric Studies Subsection to ADVERSE REACTIONS Section *1.2.c, p13-14*** The sponsor proposes to add the following Pediatric Studies Subsection: "In two placebo-controlled clinical trials of DETROL LA Capsules, 710 pediatric patients ages 5 to 10 years were treated with DETROL LA (n=486) or placebo (n=224). Patients were treated with DETROL LA 2 mg for 12 weeks. The overall frequency of adverse experiences was almost identical in the DETROL LA and placebo treatment groups (48% and 49%, respectively). Urinary tract infection was the most common adverse event occurring at a rate greater than placebo reported by pediatric patients receiving DETROL LA. Dry mouth was only reported in 0.8% of patients treated with DETROL LA and in 1.8% of patients receiving placebo. A serious adverse event was reported by 1% (n=6) of pediatric patients receiving DETROL LA and 1% (n=2) of patients receiving placebo. "The frequency of discontinuation due to adverse events was 3% for both the DETROL LA and placebo treatment groups. Table 5 lists the adverse events reported in 1% or more of pediatric patients treated with DETROL LA 2 mg once daily in the 12-week studies."	

Table 5. Incidence* (%) Of Adverse Events Exceeding Placebo Rate And Reported In ≥1% Of Pediatric Patients Treated With DETROL LA (2 mg once daily) in Two 12-Week, Phase 3 Clinical Trials

Body System	Adverse Event	%DETROL LA (n=486)	%Placebo (n=224)
Gastrointestinal disorders	Abdominal pain	5	3
	Vomiting	4	2
	Diarrhea	3	1
	Constipation	2	1
Infections and infestations	Urinary tract infection	7	4
	Ear infection	1	0
Psychiatric disorders	Abnormal behavior	2	0
Respiratory, thoracic, and mediastinal disorders	Rhinitis	2	0

*in nearest integer.

Sponsor Proposed Changes to Revision date

The sponsor proposes to change the revision date listed at the very end of the physician insert from: "Revised July 2003

818 229 006"

To: "Revised Month Year"

Format of reports to be submitted: A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guidelines for structure and content of clinical study report. The final study report will address the issues outlined	**Format of reports submitted:** The final study report format is acceptable.	**Yes**

in this request with full analysis, assessment, and interpretation.		
Timeframe for submitting reports of the studies: Amended March 3, 2003 On or before October 15, 2003	**Date study reports were submitted:** October 14, 2003	**Yes**
Additional information: **<u>Critical analysis:</u>** 1. Provide a critical analysis of urodynamic data in adults with overactive bladder treated with tolterodine and perform a subset analysis of this data in adults with detrusor hyperreflexia. This will be submitted with the final study reports. The analysis will review clinical trial data and the published literature and will describe the dose-effect (urodynamic) of tolterodine in this population.	**<u>Critical analysis:</u>** *5.3.5.4.1* <u>Methods:</u> *5.3.5.4.1, p5* Tolterodine clinical development program reviewed and MEDLINE and BIOSIS Previews searched • All citations for "tolterodine" • MESH search for "tolterodine" with "children," "cystometric measurement" and "urodynamic tests" 1. Adult studies identified (9 conducted by the sponsor, 1 by an investigator): *5.3.5.4.1, p6* • One phase 1 study on tolterodine IR in healthy males – descriptive data reported • Five phase 2 studies on tolterodine IR in adults with detrusor hyperreflexia and detrusor instability – pooled data show significant dose-response relationship for volume at first detrusor contraction, maximum cystometric capacity and PVR urine volume; data from individual studies is inconsistent in significance. • One phase 2 study on tolterodine PR in adults with OAB – found significant dose-response relationship for PVR urine volume only	**1. Yes**

	• Two phase 3 studies on tolterodine IR: o one in adults with detrusor hyperreflexia and detrusor instability – found significant increase in volume at first detrusor contraction and maximum cystometric capacity in tolterodine 2 mg v. placebo, and in PVR urine volume in tolterodine 1 or 2 mg v. placebo o one in adults with OAB and bladder outlet obstruction – found significant increase in volume at first detrusor contraction, maximum cystometric capacity and in PVR urine volume in tolterodine 2 mg v. placebo, without adverse effect on urinary flow, detrusor muscle function or incidence of urinary retention • One investigator-initiated study on tamsulosin (an alpha-blocker) with or without tolterodine IR in adults with detrusor instability with bladder outlet obstruction – found significant improvement in maximum unstable contraction pressure and volume at first unstable contraction in tamsulosin + tolterodine group. <u>Conclusions:</u> A total of 1138 patients studied. Positive dose-response relationship seen in pooled data from four phase 2 studies on tolterodine IR. Optimal dose not identified.	
2. Provide a critical analysis of tolterodine safety in pediatric patients including data from clinical trials and published literature. This will be submitted with the final study reports.	2. Pediatric studies identified from the literature: *5.3.5.4.1, p42-44* • A prospective open-label study of tolterodine IR in children with dysfunctional voiding who previously failed to tolerate oxybutynin - found comparable efficacy and improved tolerability of tolterodine • An open-label, non-randomized parallel group of tolterodine IR v. tolterodine PR v. oxybutynin in children with non-	**2. Yes**

	neurogenic diurnal urinary incontinence and symptoms of OAB - found tolterodine IR less efficacious than 2 comparators in reduction of incontinence; oxybutynin more effective in complete resolution of incontinence; no difference in rate of anticholinergic AEs • An open-label, non-randomized sequential dose-escalation study of tolterodine IR in children with OAB – descriptive data reported (13 of 33 had "possibly related" AEs, 2 withdrew due to AEs) • A retrospective chart review of tolterodine IR in children with dysfunctional voiding – descriptive data reported (4 of 30 reported AEs, 1 withdrew due to AE) • A prospective, non-randomized study of tolterodine IR in children with detrusor hyperreflexia – found no significant difference between urodynamic effects of tolterodine v. historical use of oxybutynin, other descriptive data reported Conclusions: A total of 251 children studied. Methodological limitations. No unexpected adverse events. Four studies compared AEs to oxybutynin – in three tolterodine was better tolerated, in the fourth, it was similar. 3. Pediatric clinical trials conducted by sponsor: *2.7.4* The sponsor also reviewed clinical safety data from all pediatric clinical trials conducted by sponsor [*2.7.4*]. These include all 8 pediatric studies submitted in support of this efficacy supplement (Studies 001, 002, 003, 008, 020 and 021 submitted in response to the Written Request and Studies 018 and 044 submitted outside of the Written Response). These trials included 595 children treated with varying doses and formulations of tolterodine; of these 486	

	were treated with extended release tolterodine in the two 12-week Phase 3 randomized clinical trials. Serious adverse events were also reported as of 7/15/03 in three ongoing pediatric trials (Study 009, an open label extension of Study 008; Study 006, an open label extension of Studies 001-003; and Study 007, an open label study of tolterodine oral solution). In all studies, safety evaluation included enumeration of withdrawals, adverse events and serious adverse events. Clinical laboratory data was evaluated in all studies except 008, and ECG parameters in all studies except 008 and 021. Postvoid residual urine volume was assessed in all studies except 001, 002 and 003; vital signs were obtained in all except 018 and 021. Gastrointestinal function was specifically evaluated in studies 001, 002 and 003.	

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/s/

Lisa Soule
12/23/03 10:41:49 AM
MEDICAL OFFICER

George Benson
12/23/03 11:13:09 AM
MEDICAL OFFICER

Medical Officer's Filing Memo

To:	Dan Shames, MD Director, HFD-580
Through:	George Benson, MD Team Leader, HFD-580
From:	Lisa M. Soule, MD Medical Officer, HFD-580
Date:	November 25, 2003
Re:	NDA 21-228 SE8-006 Detrol LA® (Tolterodine tartrate) NDA 20-771 N-000-C Detrol (Tolterodine tartrate) Pfizer Inc. Correspondence Date: October 10, 2003 Date Received: October 14, 2003

Current submission:

A Written Request (WR) letter dated January 23, 2001 asked Pfizer Inc. to perform four pediatric studies with tolterodine tartrate and to prepare two critical analyses. In the current electronic submission **SE8-006,** the sponsor has responded to the WR by submitting:

- a final study report, 583E-URO-0581-001 (Study #1 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study of tolterodine syrup (immediate release) in 8 patients ages one month to 4 years, with detrusor hyperreflexia due to neurogenic conditions),

- a final study report, 583E-URO-0581-002 (Study #2 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study of tolterodine syrup (immediate release) in approximately 15 patients ages five to ten years, with detrusor hyperreflexia due to neurogenic conditions),

- a final study report, 583E-URO-0581-003 (Study #3 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study of tolterodine extended release capsules in approximately 15 patients ages eleven to fifteen years, with detrusor hyperreflexia due to neurogenic conditions),

- three final study reports, 583E-URO-0084-020, DETAPE-0581-008 and 583E-URO-0084-021 [Study #4 in the Written Request, a 12-week double-blind, two parallel group, placebo-controlled randomized clinical efficacy, pharmacokinetic and safety study of

tolterodine extended release capsules with a minimum 12-week safety extension study in approximately 300 patients (to ensure a minimum of 100 patients completing 24 weeks of treatment) ages five to ten years, with overactive bladder], and

- two critical analyses, one of urodynamic data in adults with overactive bladder, and one of safety in pediatric patients.

The sponsor further submitted four additional studies not requested in the WR:

- a final study report, 583E-URO-0581-004, an open, randomized single-dose cross-over study evaluating relative bioavailability of beads from opened tolterodine prolonged release capsules and intact tolterodine prolonged release capsules in healthy volunteers

- a final study report, 583E-URO-0581-005, an open, randomized single-dose cross-over study evaluating relative bioavailability of tolterodine oral liquid solution (intended for commercial use), tolterodine oral liquid solution (prototype) and tolterodine immediate release tablets in healthy volunteers

- a final study report, 97-OATA-044, an open, uncontrolled safety and PK study of immediate release tolterodine 0.5, 1 and 2 mg BID in children 5-10 years of age with overactive bladder

- a final study report, 583E-URO-0084-018, an open, dose-escalation safety and PK study of tolterodine prolonged release 2 and 4 mg daily in children 11-15 years of age with overactive bladder

The filing meeting for NDA 21,228-SE8-006 is scheduled for November 25, 2003.

Reviewer's comment:
The submitted material is sufficient and adequate to allow filing of this application. See attached Filing Meeting Checklist for specific details.

While the Sponsor does not submit labeling language specific to the pediatric population in the "Indications and Usage" section nor under the "Dosage and Adminstration" section of the labeling, as described in 21 CFR 201.57(f)(9), it appears to the reviewer that there is an implied pediatric indication sought, as evidence by submission of pediatric PK data and language in the "Pediatric Use" section of the labeling. This will be a review issue.

Recommendation:
1) Recommend accepting NDA 21,228 SE8-006 for filing.

cc: Original NDA 21,228
HFD-580: D. Shames, G. Benson, L. Soule, and J. King

Attachment A

NDA: 21,228

45 Day Filing Meeting Checklist

CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA adequately indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e. appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications requested?	X		It appears to the reviewer that an implied pediatric indication is being sought in the submitted labeling.
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based	X		

ITEM	YES	NO	COMMENT
on proposed draft labeling?			
9) Has the applicant submitted line listings in a format to allow reasonable review of patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X	Foreign data primarily from Europe, New Zealand
11) Has the applicant submitted all additional required case report forms (beyond deaths and, drop-outs) previously requested by the Division)?			N/A
12) Has the applicant presented the safety data in a manner consistent with center guideline and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor submitted?	X		
16) From a clinical perspective, is this NDA fileable? If not, please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Reviewing Medical Officer / Date

Supervisory Medical Officer

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/s/

Lisa Soule
11/25/03 02:39:12 PM
MEDICAL OFFICER

I hope I did this right!

George Benson
12/1/03 12:01:26 PM
MEDICAL OFFICER

MEMORANDUM

To: **NDA 20-771** Original Amendment N-000 PB
DETROL™ (tolterodine tartrate immediate release tablets); Pharmacia & Upjohn
Submitted April 9, 2002
Received April 9, 2002

NDA 21-228 Original Amendment N-000 PB
DETROL LA™ (tolterodine extended release capsules); Pharmacia & Upjohn
Submitted April 9, 2002
Received April 9, 2002

Through: Mark Hirsch, MD
Team Leader, HFD-580

From: Brenda S. Gierhart, MD
Medical Officer, HFD-580

Date: July 18, 2002

Re: Request to change the tolterodine Written Request dated January 23, 2001

Background:
The tolterodine Written Request for pediatric studies, submitted to NDA 20-771 and NDA 21-228 and dated January 23, 2001, asked the sponsor to submit information from four studies and two critical analyses. The Written Request was amended on November 15, 2001 to correct a typographical error in Study #4 regarding the formulation to be used in the sentence discussing the number of patients to be studied.

Current submission:
In this submission, the sponsor requesting a one year extension on the timeframe for submitting reports described in the written request from December 15, 2002 to December 15, 2003. This extension is being requested based on the difficulty that has been encountered initiating, conducting, and completing Study #1, 2, and 3 as listed on the Written Request. As of March 2002, the protocol to satisfy Study #1 (583E-URO-0581-001) had enrolled 3 patients (PD/PK parameters must be obtained on a minimum of 8 patients), the protocol to satisfy Study #2 (583E-URO-0581-002) had enrolled 4 patients (approximately 15 patients are to be enrolled with a minimum of 8 patients for describing the PD/PK profile), and the protocol to satisfy Study #3 (583E-URO-0581-003) had enrolled 1 patient (approximately 15 patients are to be enrolled with a minimum of 8 patients for describing the PD/PK profile),

The sponsor also stated:

> A similar investigation of a competing antimuscarinic compound by another sponsor was conducted immediately prior to the tolterodine investigations. Tolterodine sites are reporting children who may have been willing to enter clinical investigations have already been studied in the competing agent study and are maintained on that medication, uninteresting in further testing.

Detrol (tolterodine tartrate) was approved on March 25, 1998. Detrol's exclusivity as a New Molecular Entity will expire on March 25, 2003. The Detrol patent #5382600 will expire on January 17, 2012. The Detrol patent #5559269 will expire on November 5, 2013. If sponsor does not submit the final study reports by March 25, 2003, no extension to Detrol's exclusivity will be possible. If exclusivity is granted, an additional 6 months would attach to the two patents.

Detrol LA (tolterodine tartrate extended release capsule) was approved on December 22, 2000. Detrol LA's exclusivity as a New Drug Formulation will expire on December 22, 2003. Detrol LA was only granted three years exclusivity since it was a formulation change. Detrol LA is covered under the Detrol patent #5382600, which will expire on January 17, 2012 and the Detrol patent #5559269, will expire on November 5, 2013. If the requested one year extension on the timeframe for submitting reports is granted, the sponsor will be given "defacto" continued exclusivity while their submission is considered by the Pediatric Exclusivity Board. If exclusivity is granted, an additional 6 months would attach to the two patents.

The submission was reviewed.

Reviewer's comments:

1) **The rationale for the requested change provided by the sponsor does not justify extending the timeframe for submitting reports for an additional 12 months. The Agency requested relatively few pediatric patients to be evaluated in Study #1, 2, and 3.**
2) **Recommend extending the timeframe for submitting reports for an additional 3 months to March 15, 2003.**

Recommendation:

1) The above response to the sponsor's proposed change dated April 9, 2002 to the Written Request should be combined into one amendment letter with:
   - the responses to the sponsor's proposed changes dated June 14, 2002 [i.e. to change the "Drug Information" section for Study #1 and Study #2 to correlate to the sequential dose escalation design doses (0.03, 0.06, and 0.12 mg/kg/day) employed in the two protocols they intend to submit to satisfy the Written Request for Study #1 (583E-URO-0581-001) and for Study #2 (583E-URO-0581-002)]
   - the responses to the sponsor's proposed changes dated July 15, 2002 [i.e. to change the "Drug Information" section for Study #3 to correlate to the sequential dose escalation design doses (2, 4, and 6 mg/day) employed in the protocol they intend to submit to satisfy the Written Request for Study #3 (583E-URO-0581-003)]
2) The tolterodine Written Request amendment letter (see Appendix A) should be presented to Dr. Dan Shames and to Dr. Victor Raczkowski for their consideration and approval.
3) A letter stating the amended sections of the Written Request should be sent to the sponsor.

cc: Original IND 46,169
HFD-580: D. Shames, M. Hirsch, B. Gierhart, and J. Mercier

<u>Appendix A:</u>

NDA 20-771
NDA 21-228

Pharmacia & Upjohn Company
Attention: Gregory G. Shawaryn

Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Reference is made to your correspondence dated April 9, 2002, June 14, 2002, and July ?, 2002 requesting changes to FDA's January 23, 2001, Written Request for pediatric studies for tolterodine tartrate tablets.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on January 23, 2001 and amended on November 15, 2001 remain the same.

Study #1, Drug Information:

We agree with your request to change this section to correlate to doses employed in Protocol 583E-URO-0581-001.

Therefore, we are amending the sentence that currently reads as follows:

> "The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.2-2.0 mg that will be administered orally in divided doses."

to

> "The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks."

Study #1, Timeframe for submitting reports of the study:
We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

> "A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

> "A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #2, Drug Information:

We agree with your request to change the section to correlate to doses employed in Protocol 583E-URO-0581-002.

Therefore, we are amending the sentence that currently reads as follows:

> "The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.5-4 mg that will be administered orally in divided doses."

to

> "The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks."

Study #2, Timeframe for submitting reports of the study:
We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

> "A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

> "A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #3, Drug Information:

We agree with your request to change the section to correlate to doses employed in Protocol 583E-URO-0581-003.

Therefore, we are amending the sentence that currently reads as follows:

> "The patient's clinician will select the appropriate total daily dose for each patient within the range of 2-4 mg. The dose will be administered orally once daily."

to

> "The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 2 mg/day for 4 weeks, 4 mg/kg/day for four weeks, and 6 mg/kg/day for four weeks."

Study #3, Timeframe for submitting reports of the study:
We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #4, Timeframe for submitting reports of the study:
We agree with your request to change the timeframe for submitting reports of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter and the amendment dated November 15, 2001 must be submitted to the Agency on or before March 15, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

[The next four paragraphs of the letter will be identical to the letter system standard pediatric Written Request amendment form].

If you have any questions, contact Jen Mercier, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Victor Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brenda Gierhart
7/29/02 03:12:32 PM
MEDICAL OFFICER

Mark S. Hirsch
7/30/02 12:57:12 PM
MEDICAL OFFICER

MEMORANDUM

To:	NDA 20-771 (tolterodine extended release capsules) NDA 21-228 (tolterodine tartrate tablets)
Through:	Mark Hirsch, MD Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	May 21, 2002
Re:	Request for Comment (NC) Correspondence Date: April 19, 2002 Date Received: April 22, 2002

Current submission:
Relative to pediatric labeling for the various formulations of tolterodine, Pharmacia & Upjohn requests the Division's written response to 4 questions as follows:

1) Provided tolterodine extended release demonstrates statistical significance in the improvement of number of urgency incontinence episodes in the 5 to 10 year old pediatric population and that 12-week and 6-month safety data in the population are comparable to adult safety data, does the Division agree that these clinical trials will be adequate to obtain the indication, "for overactive bladder with symptoms of urge urinary incontinence, frequency and urgency" for tolterodine extended release 2 mg capsules in pediatric patients 5 to 10 years of age?

2) With the understanding that the 583E-URO-0084-018 PK trial in children 11 to 15 years of age demonstrated a PK profile of tolterodine extended release in these children similar to the previously documented adult PK profile of tolterodine extended release, does the Division agree that the safety and efficacy data of the children 5 to 10 years of age in the 583E-URO-0084-020. DETAPE-0581-008 and 583E-URO-0084-021 trials may be applied to children 11 to 15 years of age to obtain the indication, "for overactive bladder with symptoms of urge urinary incontinence, frequency and urgency," for tolterodine extended release 4 mg capsules in pediatric patients 11 to 15 year of age?

3) Does the Division agree that safety and efficacy data of tolterodine extended release in children 5 to 10 years of age may be applied to the IR formulation, such that the indication. "for overactive bladder with symptoms of urge urinary incontinence, frequency and urgency," may be obtained for tolterodine IR 1 mg BID in pediatric patients 5 to 10 years of age?

4) Does the Division agree that if tolterodine oral solution and tolterodine IR tablets have similar relative bioavailability, the indication, "for overactive bladder with symptoms of urge urinary incontinence, frequency and urgency," may be granted for tolterodine oral solution 1 mg BID in pediatric patients 5 to 10 years of age?

The submission was reviewed. The Pediatric Studies with various formulations of tolterodine are summarized in the attached Table #1.

Reviewer's comment:

1) It is premature to discuss pediatric labeling for the various formulations of tolterodine.

Recommendation:

Comment #1 should be conveyed to the sponsor in a regulatory letter.

cc: DFS NDA 21-228 and 20-771
HFD-580: Division File
HFD-580: D. Shames, M. Hirsch, B. Gierhart, and J. Mercier

Table 1: Detrol and Detrol LA Pediatric Studies

Protocol Number	**Protocol submitted to IND #/Serial #**	**Study results submitted to IND#/Serial #**	**Subject ages**	**Number of enrolled subjects**	**Type of clinical trial and drug evaluated**
CTN-97-OATA-**044**	Conducted outside an IND	46,169 Serial No. 131 (on April 5, 2000)	5-10 yrs	Completed 33	Dose escalation, open label, uncontrolled, Phase 2, PK study of **Detrol tablets** 0.5, 1, and 2 mg administered BID for 14 days (the planned 3 mg BID dose was not given); patients had urinary frequency ≥ 8 micturitions/day and/or urge incontinence at least once per week (**Non-Neurogenic**)
583E-URO-0084-**018**	56,406 Serial No. 045 (on December 5, 2000)		11-15 yrs	Planned 30; Completed 31	Phase 1/2. Dose-escalation, open label, PK and safety study of **Detrol LA** 2 and 4 mg OD for 14 days in children with detrusor hyperreflexia (**Neurogenic**)
583E-URO-0084-**021**	56,406 Serial No. 048 (on February 5, 2001)		5-15 yrs	Planned 200-240; Ongoing 275	Phase 3 open-label safety, tolerability and clinical efficacy international extension study for –018 and –020 of **Detrol LA** 2 mg or 4 mg for 12 months in children with **Neurogenic** origin from –018 and in children with **Non-Neurogenic** origin form –020. [Note: only 20 patients in –018 are eligible to continue with 4 mg capsules]
583E-URO-0084-**020**	56,406 Serial No. 050 (on February 23, 2001)		5-10 yrs	Planned 300; Completed 324	Phase 3 international, randomized (2 Detrol LA:1 placebo), double blind, clinical efficacy, safety, and Pop PK study of **Detrol LA** 2 mg OD compared to placebo in pediatric subjects with urinary urge incontinence suggestive of detrusor instability (**Non-Neurogenic**). Treatment period =12 weeks
583E-URO-0581-**001**	46,169 Serial No. 145 (on September 10, 2001) and to 56,406 Serial No. 057 (on August 20, 2001)		1 month to 4 yrs	Planned 15	Dose escalation, open label, Phase 1/2 PK/PD study of **Detrol oral solution** 0.030 mg/kg/day, 0.060 mg/kg/day, and 0.120 mg/kg/day in pediatric subjects with detrusor hyperreflexia; PK data will only be collected at the 0.060 mg/kg/day dosage. Treatment period=12 weeks
583E-URO-0581-**002**	46,169 Serial No. 145 (on September 10,		5-10 yrs	Planned 15	Dose escalation, open label, Phase 1/2 PK/PD study of **Detrol oral solution** 0.030 mg/kg/day, 0.060 mg/kg/day, and

	2001) and to 56,406 Serial No. 057 (on August 20, 2001)				0.120 mg/kg/day in pediatric subjects with detrusor hyperreflexia; PK data will only be collected at the 0.060 mg/kg/day dosage. Treatment period=12 weeks
583E-URO-0581-**003**	56,406 Serial No. 057 (on August 20, 2001)		11-15 yrs	Planned 15	Dose escalation, Phase ½ study of **Detrol LA** 2, 4, and 6 mg in pediatric subjects with detrusor hyperreflexia (**Neurogenic**). Treatment period 12 weeks.
583E-URO-0581-**006**	46,169 Serial No. 152 (on December 10, 2012) and to 56,406 Serial No. 065 (on December 10, 2001)		1 month – 16 years*	Planned 45	Open-label, Phase 3, 12 month efficacy and safety extension study of **Detrol oral solution** and **Detrol LA** 2 mg and 4 mg OD in children with detrusor hyperreflexia (**Neurogenic**); Amendment #1 changed patient population to only include subjects previously in –001, -002, and –003 studies. The dose will be chosen based on each patient's clinical efficacy response and safety profile established at each of the 3 trial dosage levels during their evaluation in the previous study.
DETAPE-0581-**008**	56,406 Serial No. 071 (on March 25, 2002)		5-10 yrs.	Planned 300	Phase 3, randomized (2 Detrol LA: 1 placebo), double blind, placebo controlled international efficacy, safety, and Pop PK study of **Detrol LA** 2 mg OD in children with symptoms of urge urinary incontinence, suggestive of detrusor instability (**Non-Neurogenic** since subjects with neurogenic origin excluded)

* Amendment #1, submitted to IND in 46,169 Serial No. 156 on February 21, 2202, changed ages to 4 months –16 years

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/s/

Brenda Gierhart
5/31/02 09:04:36 AM
MEDICAL OFFICER

Mark S. Hirsch
6/3/02 04:34:03 PM
MEDICAL OFFICER
I concur.

MEMORANDUM

To:	NDA 21-228 tolterodine extended release capsules NDA 20-771 tolterodine tartrate tablets
Through:	Mark Hirsch, MD Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Re:	Submission: PU Re: Typographical error in Written Request Correspondence date: August 20, 2001 Date Received: August 21, 2001
Date:	October 17, 2001

Current submission:
The sponsor has noted a typographical error relative to the formulation to be used in Study #4 of the Pediatric Written Request issued on January 23, 2001 for tolterodine. The formulation to be used in Study #4 is the extended release capsules and this formulation is correctly stated throughout Study #4 with the exception of the one sentence under the heading "Number of patients to be studied". In the current Written Request issued on January 23, 2001, in Study #4, under the heading "Number of patients to be studied", the formulation is incorrectly listed as follows:

Detrol® (tolterodine tartrate) syrup or tablets.

The issue has been discussed with Dr. Victor Raczkowski and we are in agreement with the sponsor that this was a typographical error. The sponsor has requested "Please confirm your agreement with our assessment".

Recommendation:
1) A letter stated the amended section of the Written Request correcting the typographical error should be sent to the sponsor.

cc: Original NDA 21-228 , NDA 20-771
HFD-580: V. Raczkowski, S. Allen, D. Shames, M. Hirsch, B. Gierhart, E. Farinas

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Gierhart
11/14/01 01:56:09 PM
MEDICAL OFFICER

Mark S. Hirsch
11/14/01 04:52:47 PM
MEDICAL OFFICER

ADDENDUM to October 11, 2000 Memorandum

To:	NDA 21-228 tolterodine prolonged release capsules
Through:	Dan Shames, MD Acting Deputy Director, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Re:	Submission: N-PG (New Proposed Pediatric Study Request) Submitted June 28, 2000
Date:	December 19, 2000

After the October 11, 2000 Memorandum regarding Submission N-PG (New Proposed Pediatric Study Request submitted on June 28, 2000) was written, the Division became aware of new scientific information regarding the submission. The new scientific information consisted of an article by Carsten Goessl et al entitled "Efficacy and Tolerability of Tolterodine in Children with Detrusor Hyperreflexia" from UROLOGY 55: 414-418, 2000 (which recommends a pediatric dose of tolterodine tartrate 0.1 mg/kg orally daily divided into two doses) and the citing of this reference in DRUGDEX DRUG EVALUATIONS by MICROMEDEX to justify their on-line recommendation of tolterodine 0.1 mg/kg as the normal pediatric dose for detrusor hyperreflexia.

A teleconference with Pharmacia and Upjohn Company was held on November 29, 2000 to discuss this new scientific information. During that teleconference, it was decided that the requested partial waiver for studies in pediatric patients younger than 5 years old for NDA-21-228 will not be granted. A partial waiver for studies in neonates (i.e. birth to one month) for NDA 21-228 will be granted since no literature documented tolterodine use in infants younger than 3 months of age. A deferment for studies in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 to 15 years) for NDA 21-228 will be granted until December 15, 2002.

In addition, Pediatric study 583E-URO-0084 will no longer be a requested pediatric study in the tolterodine Pediatric Written Request. It has been replaced with three PK, PD (urodynamic), and safety studies in pediatric patients with detrusor hyperreflexia due to neurogenic conditions with one study in each of the three age groups: ages one month to four years, ages five to ten years, and ages eleven to fifteen years.

/s/

Brenda Gierhart
12/23/00 12:12:29 PM
MEDICAL OFFICER

Daniel A. Shames
1/3/01 03:30:36 PM
MEDICAL OFFICER

ADDENDUM to October 11, 2000 Memorandum

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From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
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/s/

Brenda Gierhart
12/23/00 12:12:29 PM
MEDICAL OFFICER

Daniel A. Shames
1/3/01 03:30:36 PM
MEDICAL OFFICER

MEMORANDUM

To:	NDA 21-228 tolterodine prolonged release capsules
Through:	Dan Shames, MD Acting Deputy Director, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Re:	Submission: N-PG (New Proposed Pediatric Study Request) Submitted June 28, 2000
Date:	October 11, 2000

The June 28, 2000 submission includes:

1) The Pediatric Study Plan for the prolonged release capsule formulation of tolterodine containing the summaries of two proposed pediatric protocols:
   - 583E-URO-0084-018 (previously submitted as 583-URO-0084) tolterodine prolonged release (PR) capsules: PK/ PD, safety, open label, dose-escalating, uncontrolled, parallel study of tolterodine 2 and 4 mg PR in patients aged 11-15 years with urinary urgency and frequency. The indication listed is overactive bladder. Sponsor plans to enroll ten tolterodine PR 2 mg and twenty tolterodine PR 4 mg patients for 14 days of treatment. The primary endpoint is the AUC for the active moiety.
   - 583E-URO-0084-020 (previously submitted as 98-OATA-061) tolterodine PR capsules: Phase 3 randomized, double blind, placebo-controlled, parallel, multinational, multicenter clinical efficacy and safety trial studying tolterodine 2 mg PR qd in prepubertal patients aged 5-10 years with symptoms of urinary urge incontinence suggestive of detrusor instability. The indication listed is urge incontinence. Sponsor plans to enroll 200 tolterodine and 100 placebo subjects for 12 weeks of treatment. Primary efficacy endpoint is the change in number of incontinence episodes per week (during waking hours) after 12 weeks of treatment. Patients unable to swallow capsules will be excluded from the trial. An extension to this study (583E-URO-0084-021) is planned, however the Sponsor has not submitted any additional details.
   - A request to waive pediatric studies in patients less than 5 years of age.

2) A revised Proposed Pediatric Study Request submitted in order to obtain a written request from the Division to qualify for pediatric exclusivity. This Proposed Pediatric Study Request was previously submitted on April 12, 2000 to NDA 20-771 and has been modified after discussion with the Division on May 15, 2000. The request is for the two proposed pediatric protocols described above in 1).

It is noted that a study report for the pediatric study 97-OATA-004 tolterodine immediate release (IR) was submitted on April 12, 2000. The study was submitted before the Agency issued a Written Request and can not be used to request Pediatric Exclusivity. It was a Safety/PK study of tolterodine IR 0.5 mg (n=11), 1 mg (n=10), and 2 mg (n=12) bid in total of 33 patients aged 5-10 years with urinary frequency and/or urge incontinence. The planned 3mg bid dose was not given after one 2mg subject withdrew due to tachycardia and one 2mg subject withdrew due to disturbed accommodation

Reviewer comments on Pediatric Study Plan:

1) Recommend granting partial waiver of Pediatric Rule study requirements for neonates (birth to 1 month), infants (1 month to 2 years), and children aged younger than 5 years old. Sponsor provided reasonable justification for exclusion of certain age groups.

2) Multiple recommendations given to Sponsor were not incorporated in this submission:
   - During August 12, 1999 teleconference, Sponsor was advised that Sponsor should consider a study that is a 3-month placebo-controlled trial with 6-month follow up safety data. No specific information regarding the 6-month follow up safety data extension was provided in this submission.
   - During May 15, 2000 teleconference, Sponsor was asked to clarify what age groups and from which protocols the pediatric subjects would be included in the open-label extension study. No specific information regarding the open-label extension study was provided in this submission.
   - During August 12, 1999 teleconference, Sponsor was given guidance that sparse plasma samples should be collected from subset population in the pediatric efficacy trial. No pK sampling is planned in the efficacy trial 583E-URO-0084-020.
   - During August 12, 1999 teleconference, Sponsor was asked to consider performing population pharmacokinetic studies. No population pK studies are planned.
   - During May 15, 2000 teleconference, Division recommended for 98-OATA-061 follow-up ECGs be conducted in all pediatric subjects at steady state (visit 3). The Schedule of Events for the proposed study 583E-URO-0084-020 lists ECGs to be performed at visit 4 and only on the poor metabolisers and approximately 10% of extensive metabolisers.
   - During May 15, 2000 teleconference, Division recommended for 98-OATA-061 to add frequency and/or urgency inclusions to match the adult indication. This was not done in the proposed study 583E-URO-0084-020.
   - During May 15, 2000 teleconference, the decision was made that indication statement in pediatric subjects is anticipated to be the same as that for the adult subjects. The indication for the proposed study 583E-URO-0084-020 is not the approved indication of overactive bladder.
   - During May 15, 2000 teleconference, Sponsor agreed to keep the study 583URO0084-018 blinded, if a placebo treatment group could be omitted. Later during the same meeting, the Division recommended further safety evaluation

before titrating to a 4 mg dose. To conform to the safety request, the submitted trial is an unblinded dose-escalating study. This is acceptable.

3) Response to Agency request for information was not provided in this submission:
   - During May 15, 2000 conference, Sponsor was asked to provide a justification and references for fixed versus relative volumes, for justification and reference for formula to calculate bladder capacity, and for justification for using fixed volume in this protocol and relative volume in the 98-OATA-061 protocol. This information was not provided in this submission.

Reviewer comments on Proposed Pediatric Study Request:

1) Recruitment of patients should ensure adequate representation across the age range in the clinical trial. Excluding patients from the 5 to 10 year old pediatric age group in 583E-URO-0084-020 who are not able to swallow capsules is not acceptable since it may increase the number of subjects in the older ages. Recommend using an age appropriate formulation. A liquid formulation permitting dosing recommendations based on milligrams (mg)/kilograms (kg) up to a maximum adult dose is recommended.

Recommendation:

1) Recommend granting partial waiver of Pediatric Rule study requirements for neonates (birth to 1 month), infants (1 month to 2 years), and children aged younger than 5 years old for tolterodine prolonged release capsules.
2) Recommend a regulatory letter be sent to Sponsor with the following comments and request for information:
   - Further discussion is necessary before a Written Request could be issued. It is anticipated that the written request will require using an age appropriate formulation in the clinical efficacy and safety trials. Development of a liquid formulation permitting dosing recommendations based on milligrams (mg)/kilograms (kg) up to a maximum adult dose is recommended.
   - Recommend the following changes to 583E-URO-0084-020 Clinical efficacy and safety trial in patients aged 5-10:
     - Add population pharmacokinetic subset of patients into the trial and collect sparse pK plasma samples.
     - Add follow-up ECGs be conducted in all pediatric subjects at steady state (visit 3 or 4).
     - Add frequency and/or urgency inclusions to match the adult indication.
     - Change indication to overactive bladder.
   - Request the following information:
     - Provide specific information regarding the 6-month follow up safety data extension. Clarify what age groups and from which protocols the pediatric subjects would be included in the open-label extension study.
     - Provide a justification and references for fixed versus relative volumes, for justification and reference for formula to calculate bladder capacity, and for

justification for using fixed volume in this protocol and relative volume in the 98-OATA-061 protocol.

cc: Original NDA 21-228
HFD-580 Division File
S. Allen, D. Shames, M. Hirsch HFD-580
B. Gierhart, T. Rumble, E. Farinas HFD-580

/s/

Brenda Gierhart
12/23/00 12:09:02 PM
MEDICAL OFFICER

Daniel A. Shames
1/3/01 03:27:48 PM
MEDICAL OFFICER

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Safety Update Review

See Integrated Review of Safety, pages ---- of the Medical Officer Review.