DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-771
NDA 21-228

1/23/01

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 Proposed Pediatric Study Request submitted on June 28, 2000 for tolterodine tartrate extended release capsules to NDA 21-228.

To obtain needed pediatric information on tolterodine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following four studies and two critical analyses:

Study #1:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), 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.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

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 two weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages one month to four years

Number of patients to be studied:

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.

Study endpoints:

1. PK: appropriate analysis of tolterodine and 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. Evaluation 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 per kg)-effect (urodynamic) and concentration-effect (urodynamic)

4. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters

5. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is tolterodine syrup. It is currently not a commercially available formulation. The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.2–2 mg that will be administered orally in divided doses.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max}, and 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. 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.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline 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.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #2:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), 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.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

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 two weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages five to ten years

Number of patients to be studied:

Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.

Study endpoints:

1. PK: appropriate analysis of tolterodine and 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: dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)

4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinence episodes per day

5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters

6. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following currently commercially not available formulation: tolterodine syrup. 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.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max}, and 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.

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.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline 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.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #3:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), 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.

3. To evaluate the effect and safety of tolterodine tartrate extended release capsules in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

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 two weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages eleven to fifteen years

Number of patients to be studied:

Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.

Study endpoints:

1. PK: appropriate analysis of tolterodine and 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 per kg)-effect (urodynamic) and concentration-effect (urodynamic)

4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinence episodes per day

5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters

6. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following commercially not yet available formulation: tolterodine extended release capsules. 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.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max}, and 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.

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.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline 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.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #4:

Type of study:

Clinical efficacy, PK, and safety study in patients with overactive bladder

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.

Indication:

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.

Age group in which study will be performed:

Ages five to ten years

Number of patients to be studied:

Enroll approximately 300 patients, with approximately equal number or 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 Detrol® (tolterodine tartrate) syrup or tablets.

Study endpoints:

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 tolterodine and DD 01 metabolite data.

2. Dose-response: characterization of dose(in mg per 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

Drug information:

The drug product to be used in this study is the following formulations: tolterodine extended release capsules, 2 mg, administered orally once a day in the morning.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents (e.g. constipation, dry mouth).

Statistical information:

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 DD01 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.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline 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.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent

protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Critical Analyses:

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.

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.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Evelyn R. Farinas, R. Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

Victor Raczkowski, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research