Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Almotriptan Malate
NDA:	21-001 (S-018)
PRODUCT (Brand Name):	AXERT®
DOSAGE FORM:	Oral Tablets
STRENGTHS:	12.5 mg
INDICATION:	Acute Treatment of Migraine with or without Aura (b) (4)
SUBMISSION TYPE:	Pediatric Supplement, Standard
SUBMISSION DATE:	10/31/2008
SPONSOR:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
REVIEWER:	Sripal R. Mada, Ph.D.
TEAM LEADER:	Veneeta Tandon, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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EXECUTIVE SUMMARY

AXERT® (almotriptan malate) is a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist. AXERT for oral administration contains almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan.

AXERT tablets (N 21-001) was originally approved on May 07th 2001 for oral tablet of 6.25 mg and 12.5 mg strengths for the acute treatment of migraine with or without aura in adults. Development of almotriptan tablets was performed under IND 053854. The sponsor is seeking an indication for acute treatment of migraine with or without aura in adolescent patients 12 to 17 years of age. On October 31st 2008, the sponsor submitted a supplemental NDA to fulfill the requirement of the written request (WR), for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12 to 17 years). The sponsor submitted proposed draft label in PLR format. The amended labeling includes changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use and CLINICAL PHARMACOLOGY, Pharmacokinetics section of the full prescribing information.

The sponsor submitted the following pediatric clinical study reports according to their pediatric plan in order to fulfill the required pediatric study commitments for PREA (Pediatric Research Equity Act):

- One single dose pediatric PK study (12.5 mg, study: 638-CNS-0059-014)
- One efficacy dose ranging study (6.25 – 25 mg, study: 638-CNS-0059-015)
- One long term safety study (12.5 mg, study: CAPSS-368)

The clinical pharmacokinetic study, 638-CNS-0059-014 was conducted in adolescents. The study was designed to compare the pharmacokinetics of almotriptan 12.5 mg in adolescents and adults as specified by the original PWR. It was conducted in male and female adolescent (ages 12-17 years) and adult (ages 18-55 years) subjects with or without a history of migraine. Thirty-six (36) subjects were enrolled in the study: 18 adolescents and 18 adults. Subjects received a single oral dose of almotriptan 12.5 mg after an overnight fast. Urine and blood samples were collected over a 24-hour period for pharmacokinetic assessment. The primary pharmacokinetic endpoints include plasma almotriptan C_{max} and AUC. The secondary endpoints include plasma almotriptan T_{max}, λ_z, $T_{1/2}$, CL_{po}, CL_R, V_{ss}/F, F_e% (fraction drug recovered in urine). Spontaneous and observed AEs were recorded during this period. The ratio of the geometric means (adolescents vs. adults) of pharmacokinetic parameters for almotriptan and 90% confidence intervals were obtained and evaluated based on the bioequivalence limits of 80-125%.

A. Recommendations

Office of Clinical Pharmacology has reviewed the Phase I PK study (Study 638-CNS-0059-014) in this submission and finds the study report acceptable from a clinical pharmacology and biopharmaceutics perspective, providing satisfactory agreement is reached between the sponsor and the Division regarding the final labeling languages. Detailed labeling recommendations by OCP for the language changes are provided in labeling section of the review starting page 11.

The Recommendations and labeling changes pertinent to the Clinical Pharmacology and Biopharmaceutics should be conveyed to the Sponsor.

B. Phase IV Commitments

None

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The aim of the clinical pharmacology program was to demonstrate the PK differences of almotriptan in adolescents and adults after the single oral dose. The PK of almotriptan was characterized in the Phase I PK study (Study 638-CNS-0059-014) in both populations after a single 12.5 mg oral dose of AXERT.

Pharmacokinetics of almotriptan in adolescents vs. adults:

Over all the mean pharmacokinetic parameters in adolescents was similar to that in adults as described below:

- Almotriptan mean C_{max} following administration of 12.5 mg almotriptan tablets in adolescents was higher by 2%, compared to adults.
- The mean AUC_{0-24} following administration in adolescents was lower by 9%, compared to adults. The AUC of three adolescents were lower than in adults. These three subjects also exhibited higher clearance. The clinical significance of this decrease in exposure in high body weight subjects was evaluated by the Review Statistician. Body weight did not impact the effectiveness analysis in the adolescents.
- The mean AUC_{0-inf} following administration in adolescents was lower by 10%, compared to adults.
- No change in the T_{max} and $T_{1/2}$ following administration of 12.5 mg almotriptan tablets in adolescents and adults.
- The oral clearance (CL_{PO}) following oral administration of 12.5 mg almotriptan tablets in adolescents was 11% higher compared to adults.
- No change in the fraction of almotriptan excreted in the urine (F_e %) following administration of 12.5 mg almotriptan tablets in adolescents and adults, with about 36% of the dose excreted via urine during the first 24 hour period. In general about 40-50% of the almotriptan dose is recovered unchanged in urine via active tubular secretion.

Sripal R. Mada, Ph.D.
Reviewer,
Neurology Drug Products, DCP-1, OCP

Concurrence: Veneeta Tandon, Ph.D.
Acting Team Leader
Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 21-001 (S-018)
CSO/L. Chen
/ATL Clin Pharm/Veneeta Tandon
/DDD Clin Pharm/Ramana Uppoor
HFD-860 /DD DCP-1/Mehul Mehta

1. QUESTION BASED REVIEW

A. General Attributes of the Drug

What pertinent regulatory background or history contributes to the current assessments of this drug?

AXERT tablets (N 21-001) was originally approved on May 07th 2001 for oral tablet of 6.25 mg and 12.5 mg strengths for the acute treatment of migraine with or without aura in adults. Development of almotriptan tablets was performed under IND 053854. The sponsor is seeking an indication for acute treatment of migraine with or without aura in adolescent patients 12 to 17 years of age. On October 31st 2008, the sponsor submits a supplemental NDA to fulfill the requirement of the written request (WR), for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12 to 17 years). The sponsor submitted proposed draft label in PLR format. The amended labeling includes changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use and CLINICAL PHARMACOLOGY, Pharmacokinetics section of the full prescribing information.

What are the proposed mechanism(s) of action and therapeutic indication(s)?

Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F} receptors. Almotriptan has weak affinity for 5-HT_{1A} and 5-HT_7 receptors, but has no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites.

What are the proposed dosages and route of administration?

AXERT is supplied as white, coated, circular, biconvex tablets, containing 6.25 mg and 12.5 mg dose strengths of almotriptan.

B. General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted the following pediatric clinical study reports according to their pediatric plan in order to fulfill the required pediatric study commitments for PREA (Pediatric Research Equity Act):

- One single dose pediatric PK study (12.5 mg, study: 638-CNS-0059-014)
- One efficacy dose ranging study (6.25 – 25 mg, study: 638-CNS-0059-015)
- One long term safety study (12.5 mg, study: CAPSS-368)

Among these studies, the single dose PK study (638-CNS-0059-014) was designed to demonstrate the PK characteristic of almotriptan after single oral dose in adolescents as compared to that seen in adults. The 12.5 mg dose was selected based on the efficacy results shown previously in adult migraineurs and has been used in an efficacy study in adolescents using an oral formulation of almotriptan. The design features of these pediatric clinical studies are summarized in the following table:

Study Number (Sponsor) Principal Investigator (Country) Start / End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex: M/ F Age (yr): Mean (Range) Race (W/ B/ Ot/ NR)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Healthy Subject and Initial Tolerability Studies				
638-CNS-0059-014 (Pharmacia) Bruce Brazina, MD (USA) 10 November 2001 / 12 December 2001 Synopsis	Phase 1, single-center, open-label, single-oral-dose, parallel-group design to compare the pharmacokinetics and safety of almotriptan in adolescent (12-17 yrs) and adult (18-55 yrs) subjects with or without a history of migraine.	Adolescents - 18 Sex: 9/ 9 Age: 14.9 (12-17) Race: 10/ 4/ 0/ 4 Adults - 18 Sex: 9 / 9 Age: 37.0 (18-53) Race: 14/ 1/ 1/ 2	Fixed dose Almotriptan: 12.5 mg/ single dose Oral Commercial or supplier lot: 03HAR	Completed Full report Module 5.3.3.1 CRF
Efficacy and Safety Controlled Clinical Studies				
638-CNS-0059-015 (Almirall Prodesfarma, SA; Ortho-McNeil Pharmaceutical, Inc) 93 Investigators (Argentina, Colombia, Mexico, USA) 22 July 2003 / 29 April 2005 Synopsis	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging design to evaluate efficacy and safety of almotriptan for migraine attack in adolescents (12-17 yrs). Subjects with a history of migraine with or without aura and whose attacks usually persisted for >4 hrs when untreated and occurred at intervals >24 hrs were randomized to 4 treatment arms: placebo, almotriptan 6.25, 12.5, and 25 mg within 2 age strata: 12-14 yrs and 15-17 yrs. Subjects treated a single (first) migraine attack within 4 hrs of onset. Primary endpoint: headache pain relief at 2 hrs, with photophobia, phonophobia, and nausea as co-primary endpoints.	Placebo - 172 Sex: 63/ 109 Age: 14.4 (12-17) Race: 129/ 28/ 13/ 2 Almotriptan 6.25 mg - 180 Sex: 76/ 104 Age: 14.4 (12-17) Race: 132/ 33/ 13/ 2 Almotriptan 12.5 mg - 182 Sex: 80/ 102 Age: 14.2 (12-17) Race: 142/ 26/ 13/ 1 Almotriptan 25 mg - 186 Sex: 71/ 115 Age: 14.4 (12-17) Race: 136/ 34/ 15/ 1	Fixed dose Almotriptan: 6.25, 12.5, or 25 mg/ single dose Oral Batch numbers Almotriptan 6.25 mg: 4CG2324 Almotriptan 12.5 mg: 4GG3268	Completed Full report Module 5.3.5.1 Patient profiles CRFs

Study Number (Sponsor) Principal Investigator (Country) Start / End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex: M/ F Age (yr): Mean (Range) Race (W/ B/ Ot/ NR)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Uncontrolled Clinical Studies				
CAPSS-368 (Ortho-McNeil Neurologics, Inc.[a]) 55 Investigators (USA) 23 December 2005 / 19 December 2007 Synopsis	Phase 3b, multicenter, open-label design primarily to evaluate the long-term (12 months) safety of almotriptan in the treatment of multiple migraine episodes in adolescents (12-17 yrs). Efficacy was assessed as a secondary objective. Subjects with a history of migraine headache with or without aura were enrolled. Subjects treated all migraine headaches or attacks with almotriptan 12.5 mg for up to 12 months.	Almotriptan 12.5 mg - 420 Sex: 187/ 233 Age: 14.4 (12-17) Race: 346/ 67/ 7/ 0	Fixed dose Almotriptan: 12.5 mg for multiple migraine episodes, self-administered preferably within 1 hr of onset, no more than 2 doses within 24 hrs/ up to 12 months Oral Batch numbers: R13641, 6MG520, and R13934	Completed Full report Module 5.3.5.2 Patient profiles CRFs

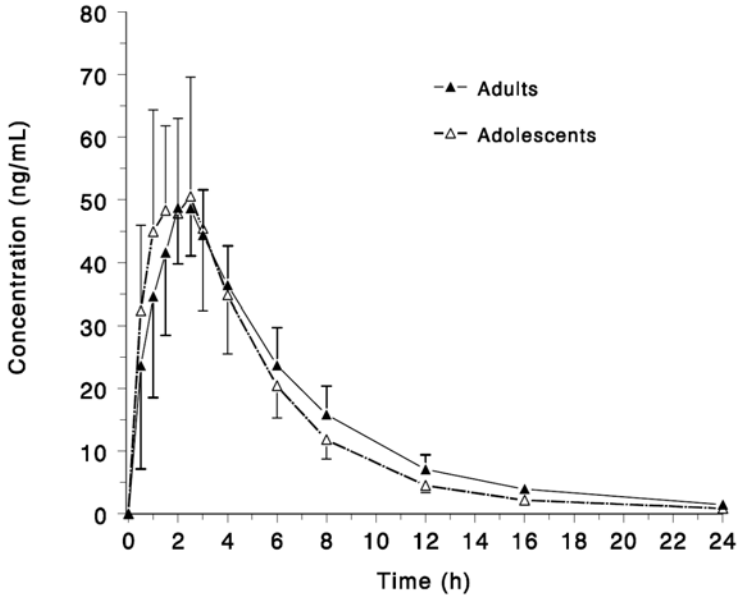
[a] The study protocol was developed and initiated under Ortho-McNeil Neurologics Inc. and was completed under the company Ortho-McNeil Janssen Scientific, LLC. The study sponsor is Ortho-McNeil-Janssen Pharmaceuticals, Inc. All three entities are part of the Johnson & Johnson family of companies.

KEY: B=Black; F=female; hr = hour; M=male; NR=not reported; Or=other; W=White; yr=year.

What is the pharmacokinetics property of almotriptan following a single oral dose of 12.5 mg AXERT tablet?

The pharmacokinetics of almotriptan was determined following a single oral dose of 12.5 mg AXERT to adolescent and adult migraineurs in Study 638-CNS-0059-014. The plasma and urine samples for pharmacokinetic determination were collected up to 24 hours post-dose at specified time points.

The figure below shows the comparison of plasma concentrations of almotriptan for all adolescents and adults following single oral dose of 12.5 mg AXERT.



The table below shows the comparison of pharmacokinetics of almotriptan for all adolescents and adults following single oral dose of 12.5 mg AXERT.

Parameter	Adolescents (N=18)	Adults (N=18)	ANOVA p-value*	Point Estimate and 90% CI †
$AUC_{0-\infty}$ (ng•h/mL)	320.4 ± 76.8 (187.7 – 500.2)	350.8 ± 56.3 (274.5 – 457.6)	.184	90.0 80.2 – 101
AUC_{0-24} (ng•h/mL)	312.4 ± 75.4 (182.1 – 496.2)	339.2 ± 54.3 (263.1 – 442.3)	.229	90.7 80.8 – 102
C_{max} (ng/mL)	55.3 ± 19.0 (32.0 – 113)	52.4 ± 8.4 (39.2 – 70.3)	.564	102 89.3 – 117
t_{max} (hr)	1.9 ± 0.7 (0.5 – 3.0)	1.9 ± 0.7 (0.5 – 3.0)	.828	104 80.4 – 135
λz (h^{-1})	0.147 ± 0.046 (0.082 – 0.277)	0.139 ± 0.025 (0.095 – 0.192)	.539	103 89.5 – 118
$t_{1/2,z}$ (h)	5.1 ± 1.5 (2.5 – 8.5)	5.1 ± 0.9 (3.6 – 7.3)	.978	NC
CL_{PO} (L/h)	41.2 ± 10.2 (25.0 – 66.6)	36.5 ± 5.8 (27.3 – 45.5)	.099	111 99.1 – 125
CL_{PO} (L/h/kg)	0.672 ± 0.127 (0.466 – 0.916)	0.518 ± 0.144 (0.301 – 0.795)	.0017	132 116 – 151
CL_R (L/h)	15.5 ± 5.7‡ (9.3 – 31.7)	14.4 ± 2.9 (9.2 – 19.8)	.462	90.7 68.4 – 120
CL_R (L/h/kg)	0.261 ± 0.115‡ (0.136 – 0.641)	0.200 ± 0.043 (0.125 – 0.276)	.041	108 80.2 - 145
Vss/F (L/kg)	3.71 ± 0.78 (2.63 – 4.95)	3.36 ± 0.84 (2.21 – 5.45)	.200	NC
Fe%	36.5 ± 4.6§ (29.6 – 43.7)	36.6 ± 9.3 (19.2 – 52.9)	.982	NC

* p-value for group differences
† 90% CI for Ln-transformed parameters, adult=reference.
‡ N=17.
§ N=9. The 24-hour cumulative excretion is reported.
Abbreviations: NC=Not calculated.

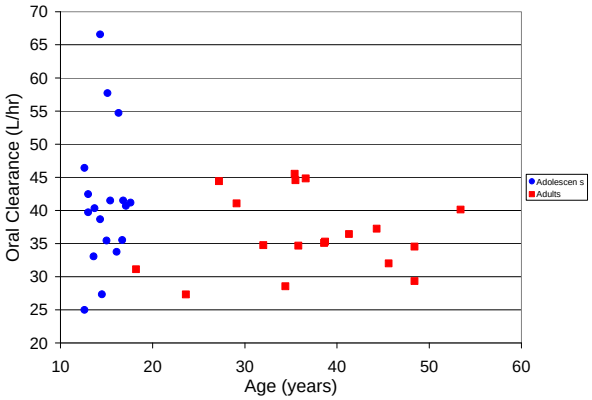
Are there significant differences in almotriptan pharmacokinetics between adolescents and adults?

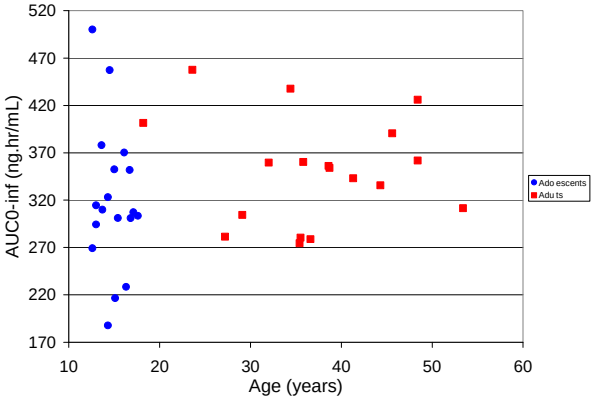
Over all, the mean pharmacokinetic parameters in adolescents were similar to that in adults as described below:

- Almotriptan mean C_{max} following administration of 12.5 mg almotriptan tablets in adolescents was higher by 2%, compared to adults.
- The mean AUC_{0-24} following administration in adolescents was lower by 9%, compared to adults.
- The mean AUC_{0-inf} following administration in adolescents was lower by 10%, compared to adults.
- No change in the T_{max} and $T_{1/2}$ following administration of 12.5 mg almotriptan tablets in adolescents and adults.
- The oral clearance (CL_{PO}) following oral administration of 12.5 mg almotriptan tablets in adolescents was 11% higher compared to adults.

- No change in the fraction of almotriptan excreted in the urine (F_e %) following administration of 12.5 mg almotriptan tablets in adolescents and adults, with about 36% of the dose excreted via urine during the first 24 hour period. In general about 40-50% of the almotriptan dose is recovered unchanged in urine via active tubular secretion.

The individual CL_{PO} and $AUC_{0\text{-}inf}$ values are plotted against the age of the subjects ranging 12-55 years following administered with equal dose of 12.5 mg almotriptan are shown in below figures.





There were 3 outliers that had lower exposure (about 45%). These subjects were the higher body weight adolescents.

We suggested the Review Statistician to assess the clinical significance of this decrease in exposure in higher body weight adolescents, by evaluating whether the high body weight adolescents showed any decrease in effectiveness as compared to the low body weight adolescents. According to the statistician no trend was observed in the effectiveness analysis based on body weight.

Are there significant differences in almotriptan pharmacokinetics in adolescents and adults between migraineurs and non-migraineurs?

Two adolescent migraineurs and 3 adult migraineurs were enrolled in the study, and the C_{max} and T_{max} in these subjects were consistent with non-migraineurs.

C. Analytical

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

The analytical method validation was acceptable. The plasma and urine levels of almotriptan were identified and measured using validated bioanalytical methods. The validated high performance liquid chromatography mass spectrometry (LC-MS/MS) using a (b) (4) (b) (4) for plasma almotriptan and validated high performance liquid chromatography (HPLC) assay using UV detection a (b) (4) nm wavelength was used for urine almotriptan estimations.

The below table shows the analytical method validation using HPLC and LC-MS/MS:

Parameter	**Almotriptan**
Plasma	
linearity	0.5 to 200 ng/mL
Inter-assay precision (%CV)	1.2 to 9.9%
Bias (%)	4.1 to 7.5%
LLOQ	0.5 ng/mL
Urine	
linearity	50 to 10,000 ng/mL
Inter-assay precision (%CV)	2.6 to 3.1%
Bias (%)	-0.8 to 0.5%
LLOQ	50 ng/mL
Reviewer Comments	These assays characteristics and specificity are satisfactory. Representative LC-MS and HPLC chromatograms studied at lower and higher QC samples are presented.

2. LABELING RECOMMENDATIONS

The labeling recommendations are given below as track changes. The changes should be conveyed to the sponsor.

FOLLOWING THIS PAGE, 33 PAGES WITHHELD IN FULL - B4 - DRAFT LABELING

APPENDICES

A. Clinical Pharmacology and Biopharmaceutics Individual Study Review

Study 638-CNS-0059-014: "Almotriptan: A Phase I Comparative Study of the Pharmacokinetics and Safety of Almotriptan in Healthy Adolescents and Adults"

Principal Investigator: Bruce Brazina, MD
Study center: (b) (4)
Study period: 10 November 2001 to 12 December 2001
Phase of development: Phase I

Objectives:

Primary:

- To evaluate and compare the PK of almotriptan between adolescents and adults.

Secondary:

- To evaluate and compare the safety of almotriptan between adolescents and adults.

Study Design	This was a single center, open-label, parallel-group design. • The intent of this study was to evaluate and compare the PK of almotriptan in the two age populations, adolescents and adults. A parallel-group design was selected. • This was not a randomized study and subjects were assigned sequential subject numbers within group in the order in which they were enrolled.
Study Population	• Healthy male and female adolescent (12-17 years) and adult (18-55 years) subjects, with or without a history of migraine. • A total of 36 subjects were included in the study. Eighteen subjects were assigned to each group. Adolescents were numbered 1-18 and adults, 19-36.
Investigational Product	12.5 mg Axert™ tablets: *Packaging lot*: (b) (4). *Commercial or supplier lot*: (b) (4). Almotriptan malate was supplied as 12.5 mg Axert™ tablets in commercial containers (blister pack of 6 tablets). The dose was expressed as the free base equivalent of almotriptan.
Dosage and Administration	<table><tr><th>Group</th><th>Drug</th><th>Form</th><th>Route</th><th>Dose</th><th>Frequency</th><th># Subjects</th></tr><tr><td>A (Adult)</td><td>Almotriptan</td><td>Tablet</td><td>Oral</td><td>12.5 mg</td><td>Once</td><td>18</td></tr><tr><td>B (Adolescent)</td><td>Almotriptan</td><td>Tablet</td><td>Oral</td><td>12.5 mg</td><td>Once</td><td>18</td></tr></table>
Sampling:	Blood: Serial blood samples were collected predose and up to 24 hours after dosing for the determination of plasma almotriptan concentrations. Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dose (13 samples). Urine: Urine samples were collected at pre-dose, 0-4, 4-8, 8-12, and 12-24 hours post-dose (5 samples).
Assay	Plasma concentrations of almotriptan by a validated LC/MS/MS method and

	urine samples by a validated HPLC assay.
Criteria for Evaluation	The primary PK endpoints include plasma almotriptan C_{max} and AUC. The secondary PK endpoints include plasma almotriptan T_{max}, λ_z, $T_{1/2}$, CL_{po}, CL_R, V_{ss}/F, F_e% (fraction drug recovered in urine). The safety endpoints include AE, clinical laboratory tests (hematology, serum biochemistry and urinalysis), vital signs, and 12-lead ECG.
Statistical Methods	PK: Pharmacokinetic parameters for almotriptan were estimated using non-compartmental methods. Descriptive statistics for almotriptan PK parameters were computed for each group and analysis of variance (GLM) was used to determine group differences in parameters. Geometric means and 90% CI for group differences in select almotriptan ln-transformed PK parameters were calculated by using the least-squares means procedure. Safety: A listing of safety laboratory assays was generated by group and summary statistics (mean, median, standard deviation, minimum, and maximum) were displayed for the observed and change-from-baseline values of each quantitative laboratory assay and vital sign variables. Listings of the abnormal quantitative lab values and all qualitative values were also provided. Adverse events were listed and tabulated by group.

Subjects and Demographics:

A total of 36 healthy male and female adolescent (N=18) and adult (N=18) subjects, participated in this study. Complete demographics of adolescent and adult subjects are presented in Table 1 and Table 2.
Sufficient number of subjects per group were enrolled to provide adequate power to detect a 20% difference between population means at p=0.05 in C_{max} and $AUC_{0\text{-inf}}$.

Table 1 Demographic data for adolescent subjects

Subject	Sex	Race	Age (yr)	Weight (kg)	Height (cm)	BMI* (kg/M^2)
1	Female	Not Listed	12.6	70.0	167.5	24.9
2	Male	Not Listed	15.1	89.5	182.0	27.0
3	Male	White	16.8	75.9	175.0	24.8
4	Male	Not Listed	16.3	76.4	179.0	23.8
5	Female	Not Listed	16.1	68.6	162.5	26.0
6	Male	Black	13.0	61.0	172.0	20.6
7	Male	White	13.7	47.7	162.5	18.1
8	Male	White	12.6	35.9	140.0	18.3
9	Male	White	14.3	52.3	169.0	18.3
10	Male	Black	13.0	67.3	182.9	20.1
11	Female	White	15.0	49.5	160.0	19.3
12	Male	Black	14.3	72.7	165.1	26.7
13	Female	Black	17.1	68.2	160.0	26.6
14	Female	White	14.5	58.6	166.4	21.2
15	Female	White	17.6	53.2	157.5	21.4
16	Female	White	15.4	47.3	162.6	17.9
17	Female	White	16.7	65.9	171.5	22.4
18	Female	White	13.6	55.9	151.1	24.5
N=18						
Mean			14.9	62.0	165.9	22.3
Standard Deviation			1.6	13.2	10.7	3.3
Minimum			12.6	35.9	140.0	17.9
Maximum			17.6	89.5	182.9	27.0

Table 2 Demographic data for adult subjects

Subject	Sex	Race	Age (yr)	Weight (kg)	Height (cm)	BMI* (kg/M^2)
19	Male	Asian	36.6	62.3	167.6	22.2
20	Female	White	35.4	57.3	161.3	22.0
21	Female	White	27.2	73.1	175.3	23.8
22	Male	White	38.6	94.0	193.0	25.2
23	Male	White	23.6	90.9	188.0	25.7
24	Female	White	48.4	56.8	163.8	21.2
25	Male	White	18.2	67.0	173.9	22.2
26	Female	Not Listed	35.8	53.1	156.2	21.8
27	Male	White	34.4	82.3	182.9	24.6
28	Female	Not Listed	32.0	56.4	160.0	22.0
29	Female	White	45.6	76.4	176.5	24.5
30	Male	White	41.3	71.4	175.3	23.2
31	Female	White	35.5	58.2	168.9	20.4
32	Male	White	53.4	89.5	176.5	28.7
33	Female	White	44.3	76.4	165.1	28.0
34	Male	Black	29.1	90.0	181.6	27.3
35	Female	White	38.7	76.4	171.5	26.0
36	Male	White	48.4	90.9	188.0	25.7
N=18						
Mean			37.0	73.5	173.6	24.1
Standard Deviation			9.1	14.0	10.4	2.5
Minimum			18.2	53.1	156.2	20.4
Maximum			53.4	94.0	193.0	28.7

Protocol deviations:

1. Two subjects (subject # 11 and # 13) violated inclusion criteria # 4, consumed a small amount of chocolate and 8 ounce of Coca Cola, about 35 hours prior to dosing.

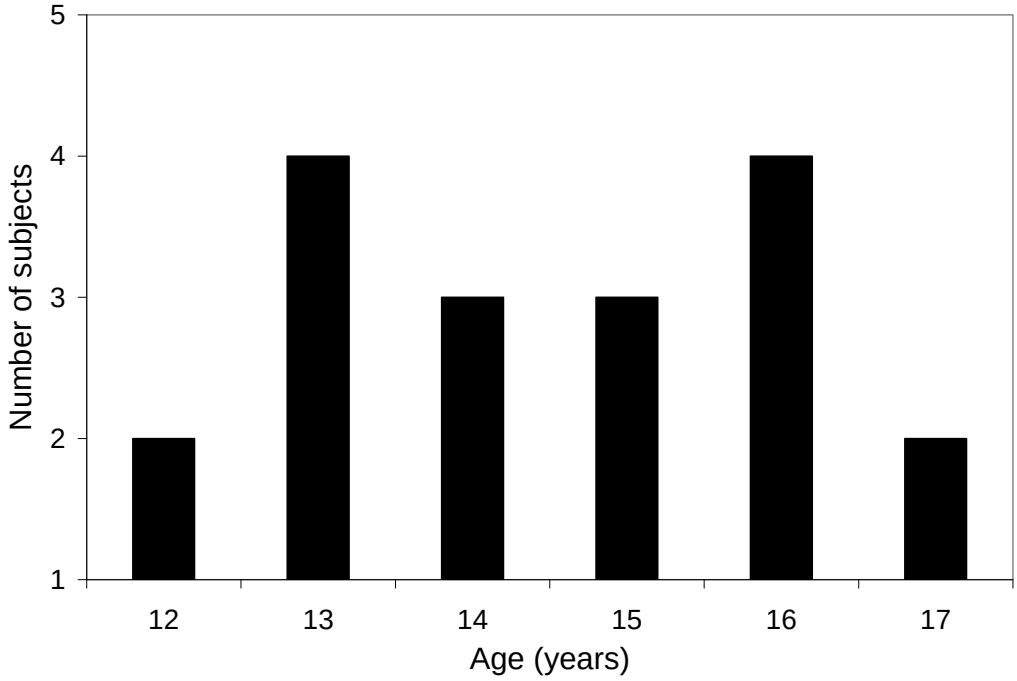
2. Instructions were incorrectly given to adolescent subjects # 10 to # 18, and urine specimens scheduled for collection following 8 hour post-dose (8-24 hour) for there subjects were incomplete.

Subjects with migraine headaches:

- Adolescent subjects # 9 and # 10 suffered (controlled baseline status) migraine headache.

- Adult subjects # 28 and # 32 (controlled baseline status), and subject # 29 (active baseline status) suffered migraine headache.

Reviewer's analysis: The following figure presents the number of adolescent subjects at each age in this study.



Assay:

Plasma concentrations of almotriptan were analyzed by using validated LC-MS/MS using a (b) (4) Urine samples were analyzed for almotriptan by validated HPLC assay using UV detection (b) (4) nm wavelength.

Plasma: The calibration curve was linear over concentration range (b) (4) ng/mL. Each batch of experimental samples was run against calibration standards. QC samples were prepared at five concentrations ((b) (4), diluted ((b) (4)) and diluted (b) (4)) ng/mL). The results calculated using peak area ratios and calibration curves generated using weighted ($1/x^2$) linear least-squares regression.

Urine: The calibration curve was linear over concentration range (b) (4) ng/mL. Each batch of experimental samples was run against calibration standards. QC samples were prepared at four concentrations (b) (4) and diluted ((b) (4)) ng/mL). The results calculated using peak area ratios and calibration curves were generated using weighted ($1/x^2$) linear least-squares regression.

The precision and accuracy for the parent compound in plasma and urine is presented in the following table.

Table 3 Method validation data using LC-MS and HPLC assays

Parameter	**Almotriptan**
Plasma	
linearity	0.5 to 200 ng/mL
Inter-assay precision (%CV)	1.2 to 9.9%
Bias (%)	4.1 to 7.5%
LLOQ	0.5 ng/mL
Urine	
linearity	50 to 10,000 ng/mL
Inter-assay precision (%CV)	2.6 to 3.1%
Bias (%)	-0.8 to 0.5%
LLOQ	50 ng/mL
Reviewer Comments	These assays characteristics and specificity are satisfactory. Representative LC-MS and HPLC chromatograms studied at lower and higher QC samples are presented.

Pharmacokinetic Results:

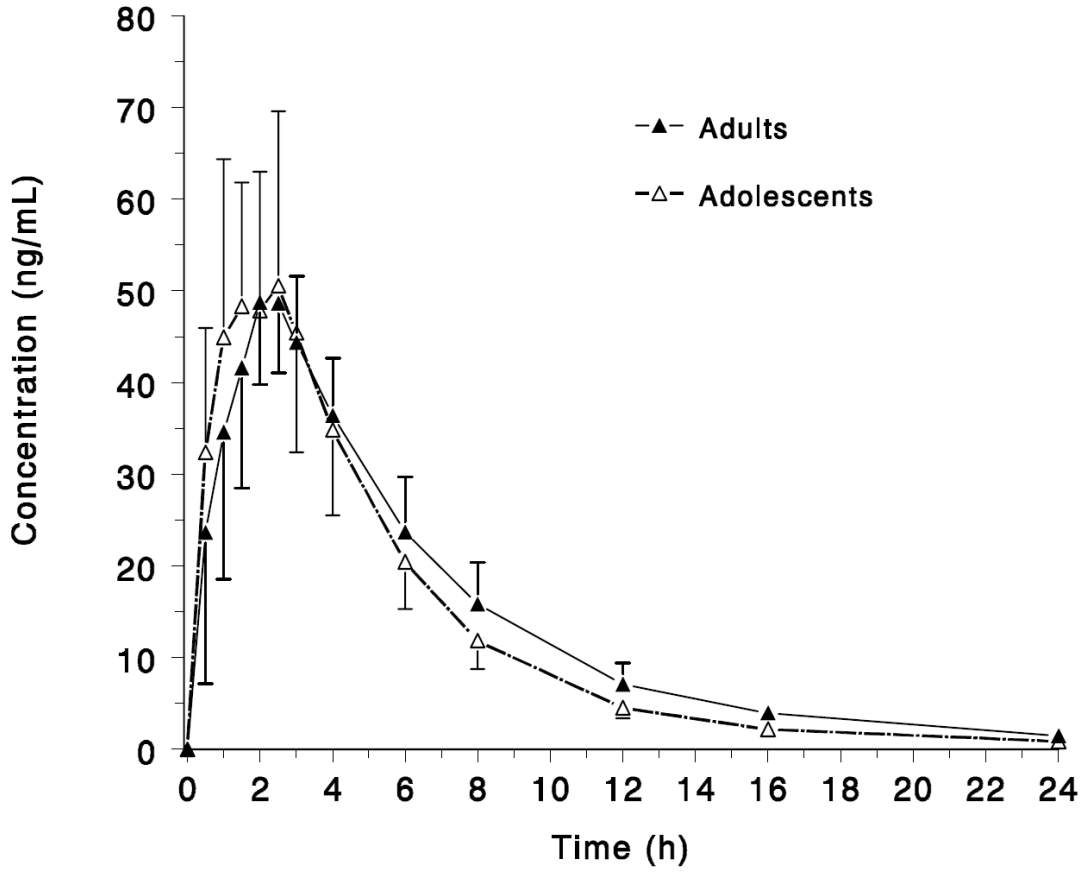
The mean almotriptan PK parameters and statistical analysis on the primary and secondary endpoints following oral administration of 12.5 mg almotriptan tablets in healthy adolescent and adult subjects are presented in Table 4.

Table 4 Summary of almotriptan PK parameters following single oral administration of 12.5 mg almotriptan to adolescents and adults

Parameter	Adolescents (N=18)	Adults (N=18)	ANOVA p-value*	Point Estimate and 90% CI †
$AUC_{0-\infty}$ (ng•h/mL)	320.4 ± 76.8 (187.7 – 500.2)	350.8 ± 56.3 (274.5 – 457.6)	.184	90.0 80.2 – 101
AUC_{0-24} (ng•h/mL)	312.4 ± 75.4 (182.1 – 496.2)	339.2 ± 54.3 (263.1 – 442.3)	.229	90.7 80.8 – 102
C_{max} (ng/mL)	55.3 ± 19.0 (32.0 – 113)	52.4 ± 8.4 (39.2 – 70.3)	.564	102 89.3 – 117
t_{max} (hr)	1.9 ± 0.7 (0.5 – 3.0)	1.9 ± 0.7 (0.5 – 3.0)	.828	104 80.4 – 135
λz (h^{-1})	0.147 ± 0.046 (0.082 – 0.277)	0.139 ± 0.025 (0.095 – 0.192)	.539	103 89.5 – 118
$t_{1/2,z}$ (h)	5.1 ± 1.5 (2.5 – 8.5)	5.1 ± 0.9 (3.6 – 7.3)	.978	NC
CL_{PO} (L/h)	41.2 ± 10.2 (25.0 – 66.6)	36.5 ± 5.8 (27.3 – 45.5)	.099	111 99.1 – 125
CL_{PO} (L/h/kg)	0.672 ± 0.127 (0.466 – 0.916)	0.518 ± 0.144 (0.301 – 0.795)	.0017	132 116 – 151
CL_R (L/h)	15.5 ± 5.7‡ (9.3 – 31.7)	14.4 ± 2.9 (9.2 – 19.8)	.462	90.7 68.4 – 120
CL_R (L/h/kg)	0.261 ± 0.115‡ (0.136 – 0.641)	0.200 ± 0.043 (0.125 – 0.276)	.041	108 80.2 - 145
Vss/F (L/kg)	3.71 ± 0.78 (2.63 – 4.95)	3.36 ± 0.84 (2.21 – 5.45)	.200	NC
Fe%	36.5 ± 4.6§ (29.6 – 43.7)	36.6 ± 9.3 (19.2 – 52.9)	.982	NC

* p-value for group differences
† 90% CI for Ln-transformed parameters, adult=reference.
‡ N=17.
§ N=9. The 24-hour cumulative excretion is reported.
Abbreviations: NC=Not calculated.

The mean concentration-time profiles following 12.5 mg almotriptan tablets in adolescent and adult subjects are presented in below figure.

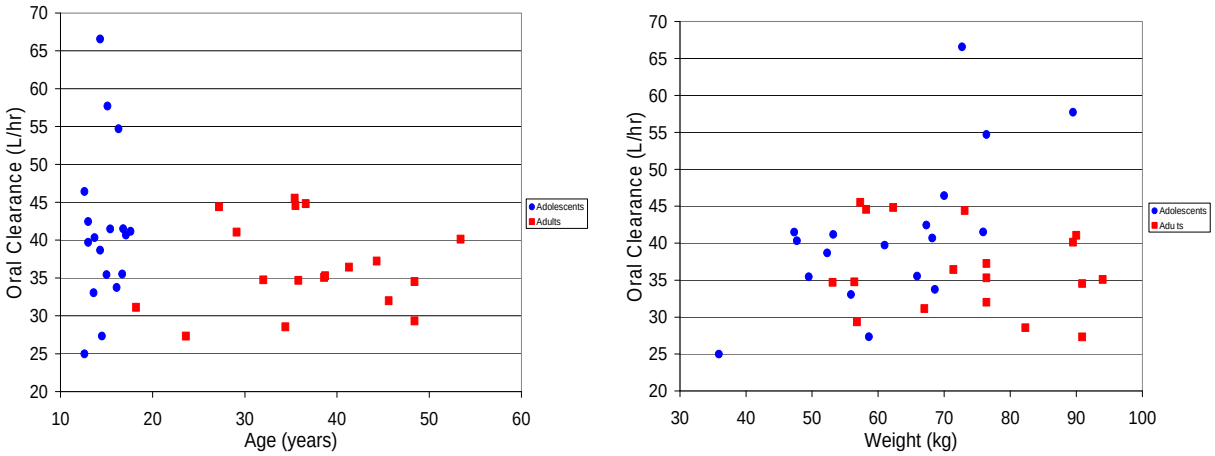


Over all the mean pharmacokinetic parameters in adolescents was similar to that in adults as described below:

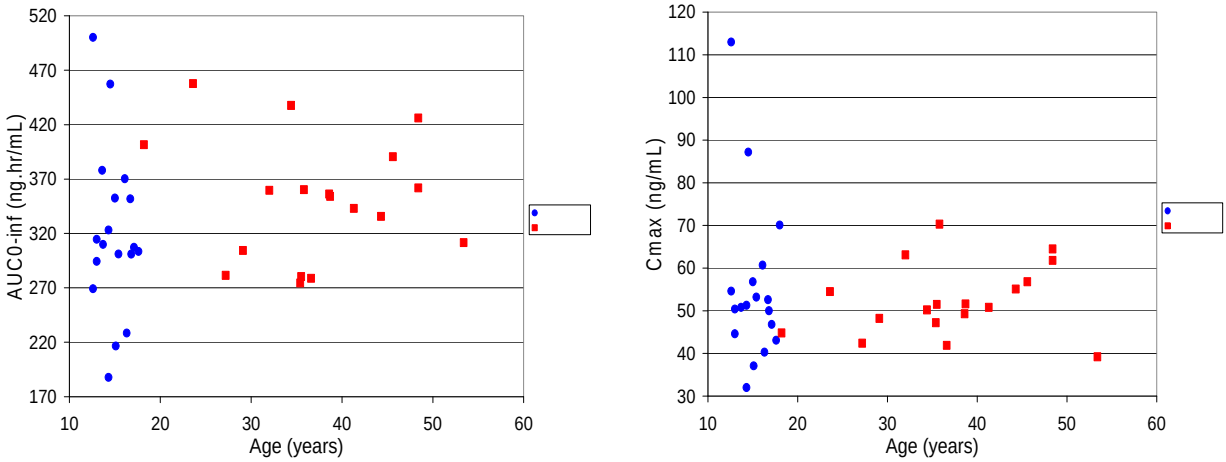
- Almotriptan C_{max} following administration of 12.5 mg almotriptan tablets in adolescents was higher by 2%, compared to adults. The C_{max} of two adolescent, (Subjects # 8 exhibited 113 ng/mL and Subject # 14 exhibited 87.2 ng/mL), exceeded the upper range in adults. These two subjects exhibited the lowest clearance of the adolescents evaluated.
- The mean $AUC_{0\text{-}inf}$ following administration in adolescents was lower by 10%, compared to adults.
- The mean $AUC_{0\text{-}24}$ following administration in adolescents was lower by 9%, compared to adults.
- No change in the T_{max} and $T_{1/2}$ following administration of 12.5 mg almotriptan tablets in adolescents and adults.
- The oral clearance (CL_{PO}) following oral administration of 12.5 mg almotriptan tablets in adolescents was 11% higher compared to adults.
- No change in the fraction of almotriptan excreted in the urine (F_e %) following administration of 12.5 mg almotriptan tablets in adolescents and adults, with about 36% of the dose excreted via urine during the first 24 hour period. In general about 40-50% of the almotriptan dose is recovered unchanged in urine via active tubular secretion.

Reviewer's Analysis:

The oral clearance (body weight not normalized) is not affected with the age ranging 12-55 years or body weight ranging 36-94 kg.

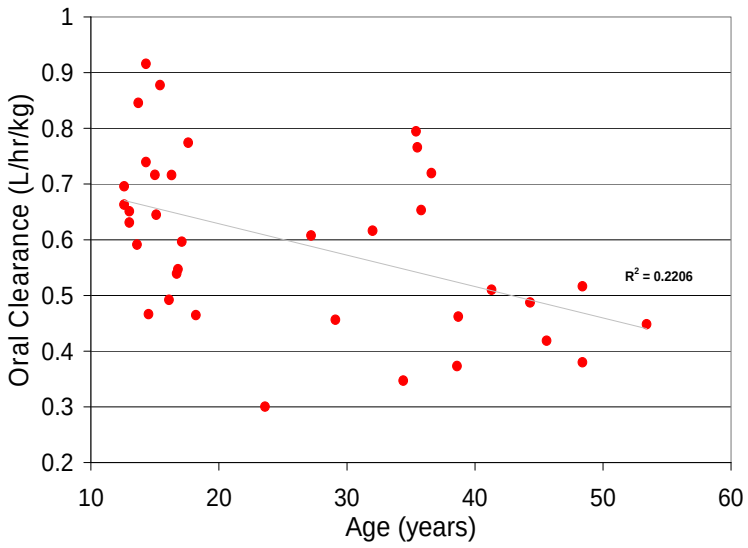


There were 3 outliers that had higher clearance. The outliers were the higher body weight adolescents. The individual $AUC_{0\text{-}inf}$ and C_{max} values are plotted against the age of the subjects ranging 12-55 years shows there is no significant change in the exposure with the age when administered with equal dose of 12.5 mg almotriptan. The 90% CI for C_{max} and $AUC_{0\text{-}inf}$ were within the acceptable limits (89-117% for C_{max} and 80-101% for $AUC_{0\text{-}inf}$).

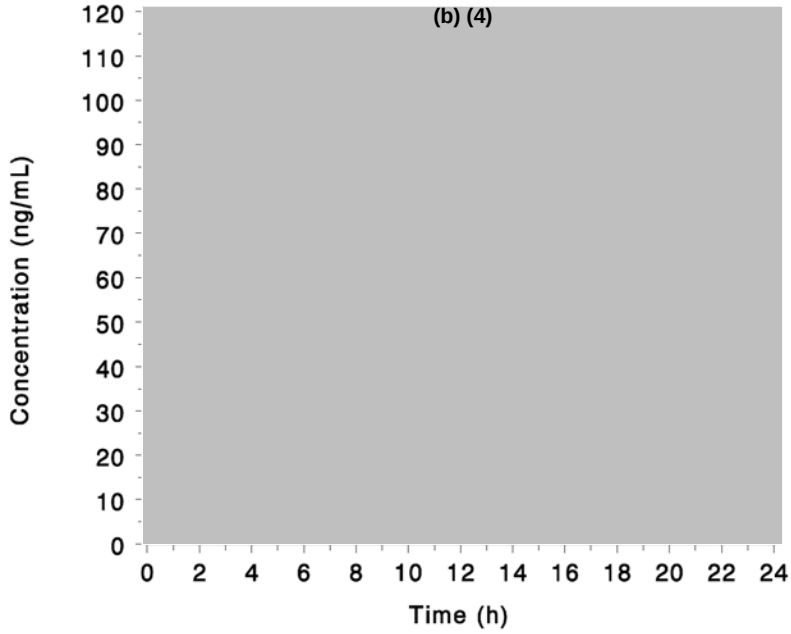


The individuals with higher clearance showed 45% decreased $AUC_{0\text{-}inf}$. According to the Review Statistician, the statistical analysis of the Effectiveness Data did not show any correlation to body weight.

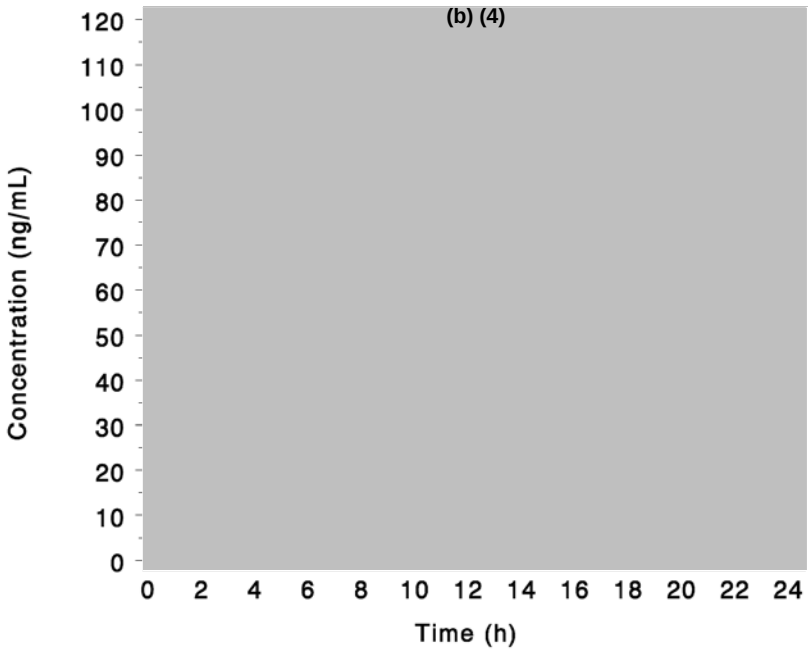
Following figure shows a decreased trend in the oral clearance (normalized body weight) with the age ranging 12-55 years. This is expected due to weight normalization of individuals.



The individual plasma concentration-time profiles following 12.5 mg almotriptan tablets in adolescent and adult subjects (with migraineurs represented stripped lines) are presented in below figures. Two adolescent migraineurs and 3 adult migraineurs were enrolled in the study, and the C_{max} and T_{max} in these subjects were consistent with non-migraineurs.



Individual plasma concentrations in adolescents (stripped lines for migraineurs)



Individual plasma concentrations in adults (stripped lines for migraineurs)

Safety:

No deaths, severe adverse effects leading to study discontinuation. Twelve adverse events reported in the 8 subjects (3 adolescents and 5 adults). One event was possibly related to study medication. A 16 year old male adolescent (Subject # 3) experienced ventricular extra-systole 3 hours after dosing almotriptan. A summary of adverse events are presented in Table 5.

Table 5 Summary of adverse events following single oral administration of 12.5 mg almotriptan to adolescents and adults

Body System Description (COSTART)	Output Term (COSTART)	Age Group			
		Group B (N = 18)		Group A (N = 18)	
		Mild	Moderate	Mild	Moderate
Cardiac disorders	Ventricular extrasystoles	1			
Gastrointestinal disorders	Dry mouth			1	
	Nausea			1	
Infections and infestations	Upper respiratory tract infection NOS			1	
Investigations	Heart rate increased	1			
Nervous system disorders	Headache NOS		1		
	Vasovagal attack			2	
Vascular disorders	Hypotension NOS	1			

* Only one occurrence per subject with maximum intensity tabulated.

Conclusions:

- Based on the results from study 638-CNS-0059-014, 12.5 mg almotriptan tablets have similar pharmacokinetics in adolescents and the adult population.
- Two adolescent migraineurs and 3 adult migraineurs were enrolled in the study, and the C_{max} and T_{max} in these subjects were consistent with non-migraineurs.
- Almotriptan $T_{max,}$ elimination half-life and fraction excretion in urine was similar following administration of 12.5 mg almotriptan tablets in adolescents and adults.

Reviewer's Comment:

- *The median T_{max} is appropriate compared to the mean T_{max}, as presented in the Table 4.*
- *The sponsor stated Vss/F as steady state volume of distribution; however this study is conducted by single dose administration. So Vss/F is not an appropriate parameter.*

B. OCPB Filing/Review Form

Office of Clinical Pharmacology

15. NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	**21-001 (S-018)**	**Brand Name**	**AXERT®**
Division	**DCP-1**	**Generic Name**	**Almotriptan malate**
Medical Division	**HFD-120**	**Drug Class**	**Antimigraine Drug**
Primary Reviewer	**Sripal R. Mada**	**Indication(s)**	**Acute Treatment of Migraine with or without Aura (b) (4)**
Team Leader	**Veneeta Tandon**	**Dosage Form**	**6.25 mg and 12.5 mg Tablet**
Date of Submission	**10/31/2008**	**Dosing Regimen**	**12.5 mg, some may benefit from 6.25 mg should not take more than 2 tablets within a 24-hour period**
Estimated Due Date of Review	**03/26/2009**	**Route of Administration**	**Oral**
PDUFA Due Date	**04/30/2009**	**Sponsor**	**Ortho-McNeil-Janssen Pharmaceuticals, Inc.**
Division Due Date	**04/09/2009**	**Priority Classification**	**S**

Clinical Pharmacology Information

Summary: This is a supplemental NDA (sNDA) to fulfill the requirement of the written request (WR) of AXERT® Almotriptan (Almotriptan malate) tablets. AXERT® was approved by FDA on May 07th 2001 under NDA 021001. Development of Almotriptan tablets was performed under IND 053854. The sponsor is seeking an indication for acute treatment of migraine with or without aura in Adolescent patients 12 to 17 years of age. The sponsor submitted proposed draft label in PLR format.

This submission includes:

- One single dose pediatric PK study (12.5 mg, study: 638-CNS-0059-014)
- One efficacy dose ranging study (6.25 – 25 mg, study: 638-CNS-0059-015)
- One long term safety study (12.5 mg, study: CAPSS-368)

A summary table of all the above studies is included in the Appendix. The clinical PK study, 638-CNS-0059-014 was conducted in adolescents. The study was designed to compare the PK of Almotriptan 12.5 mg in adolescents and adults as specified by the original PWR. It was conducted in male and female adolescent (ages 12-17 years) and adult (ages 18-55 years) subjects with or without a history of migraine. Thirty-six (36) subjects were enrolled in the study: 18 adolescents and 18 adults. Subjects received a single oral dose of Almotriptan 12.5 mg after an overnight fast. Urine and blood samples were collected over a 24-hour period for PK assessment. Spontaneous and observed AEs were recorded during this period. Laboratory safety tests, vital signs, and 12-lead ECG were performed at scheduled intervals. Pharmacokinetic parameters for Almotriptan were estimated using non-compartmental methods and summarized by age group (adolescent and adult) using descriptive statistics. Analysis of variance was used to determine between-group differences. Geometric means and 90% confidence intervals for between-group differences in selected Almotriptan Ln-transformed PK parameters were calculated using the least-squares means procedure.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any

STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			PLR conversion
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:	**-**	**-**	**-**	
Isozyme characterization:				
Blood/plasma ratio:	**-**	**-**	**-**	
Plasma protein binding:	**-**	**-**	**-**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**-**	**-**	**-**	
multiple dose:	**-**	**-**	**-**	
Patients-				
single dose:	**-**	**-**	**-**	
multiple dose:	**-**	**-**	**-**	
Dose proportionality -				
fasting / non-fasting single dose:	**-**	**-**	**-**	
fasting / non-fasting multiple dose:	**-**	**-**	**-**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**-**	**-**	**-**	
In-vivo effects of primary drug:	**-**	**-**	**-**	
In-vitro:				
Subpopulation studies -				
ethnicity:	**-**	**-**	**-**	
gender:	**-**	**-**	**-**	
pediatrics:	**X**	**1**	**-**	Single dose PK study. One Phase I comparative study of the PK and safety of Almotriptan in adolescents and adults with or without migraine. Study 638-CNS-0059-014.
geriatrics:	**-**	**-**	**-**	
renal impairment:	**-**	**-**	**-**	
hepatic impairment:	**-**	**-**	**-**	
PD:				
Phase 2:	**-**	**-**	**-**	
Phase 3:	**-**	**-**	**-**	
PK/PD:				
Phase 1 and/or 2, proof of concept:	**-**	**-**	**-**	
Phase 3 clinical trial:	**-**	**-**	**-**	
Population Analyses -				
Data rich:	**-**	**-**	**-**	
Data sparse:	**-**	**-**	**-**	
II. Biopharmaceutics				
Absolute bioavailability:	**-**	**-**	**-**	
Relative bioavailability -				
solution as reference:	**-**	**-**	**-**	
alternate formulation as reference:	**-**	**-**	**-**	
Bioequivalence studies -				
traditional design; single / multi dose:	**-**	**-**	**-**	
replicate design; single / multi dose:	**-**	**-**	**-**	
Food-drug interaction studies:	**-**	**-**	**-**	
Dissolution:	**-**	**-**	**-**	
(*IVIVC*):	**-**	-	-	
Bio-waiver request based on BCS	**-**	**-**	**-**	

BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			57 References
Total Number of Studies		**1**		
		+1 Assay		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	-	
QBR questions (key issues to be considered)	Is PK of Almotriptan comparable in adolescents and adults	
Other comments or information not included above	-	
Primary reviewer Signature and Date	**Sripal R. Mada,** Clin. Pharm. Reviewer, Neurology Products	
Secondary reviewer Signature and Date	**Veneeta Tandon,** Acting Team Leader, Neurology Products	

CC: NDA 021001 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Sripal R. Mada, Veneeta Tandon, Ramana Uppoor, Mehul Mehta)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sripal R Mada
3/18/2009 02:29:49 PM
BIOPHARMACEUTICS

Veneeta Tandon
3/18/2009 02:36:07 PM
BIOPHARMACEUTICS