**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

| | |
|---|---|
| **NDA:** | 21-450 (S-005) |
| **Brand Name:** | Zomig® Nasal Spray |
| **Generic Name:** | Zolmitriptan |
| **Sponsor:** | AstraZeneca Pharmaceuticals LP |
| **Type of Dosage Form:** | Nasal Spray |
| **Strengths:** | 5 mg |
| **Indications:** | Treatment of migraine with or without aura in adults |
| **OCP Reviewer:** | Ta-Chen Wu, Ph.D. |
| **OCP Team Leader (Acting):** | Veneeta Tandon, Ph.D. |
| **OCP Division:** | DCP-I HFD-860 |
| **OND Division:** | Division of Neurology Drug Products HFD-120 |
| **Submission Date:** | December 14, 2007<br>April 03, 2008 |
| **Type of Submission:** | Efficacy Supplement, Standard |

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## *1. EXECUTIVE SUMMARY*

Zomig® (zolmitriptan), a selective 5-HT $_{1B/1D}$ receptor agonist, was originally approved as oral tablet and orally disintegrating tablet for the acute treatment of migraine with or without aura in adults (≥18 years of age). Zomig tablet and orally disintegrating tablet contain 2.5 mg or 5 mg of zolmitriptan per tablet. Zomig® (Zolmitriptan) Nasal Spray (NDA 21-450) was originally approved on 30 September 2003 for the same indication in adults. Zomig® Nasal Spray is supplied as an aqueous solution containing 50 mg/ml zolmitriptan and is delivered by the device in a unit dose of 5 mg and is intended for a single use only.

On 14 December 2007, the sponsor submited a supplemental NDA for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12-17 years). The amended labeling involves changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use **(b) (4)** of the full prescribing information. Although, the sponsor is not seeking an indication for the use of Zomig ® (zolmitriptan) Nasal Spray for the acute treatment of migraine in adolescents based on the results of the efficacy study.

The Sponsor submits the following pediatric clinical study reports in order to fulfill the required pediatric study commitments for PREA (Pediatric Research Equity Act):

- Clinical Study Report for Pharmacokinetic Study D1221C00004
- Clinical Study Report for Efficacy Study D1221C00005
- Clinical Study Report for Safety Study 311CUS/0005 (previously submitted to NDA 20-768 on September 30, 2003)

The pharmacokinetic study (D1221C00004) was designed and conducted to establish the pharmacokinetic differences between adolescent (12-17 years) and adult (≥18 years) populations following a single 5-mg dose of zolmitriptan nasal spray between migraine attacks. The 5-mg dose was selected on the basis of efficacy and tolerability demonstrated for the approved oral tablet formulation in adults. The primary endpoint was $AUC_{inf}$ for zolmitriptan. The secondary endpoints included Cmax, AUC0-t, Tmax, t1/2 and CL/F. Similar pharmacokinetic parameters were also analyzed for the active metabolite 183C91 as secondary endpoints. There was no efficacy assessment in this study. Ratios of the geometric means (adolescent vs. adult) of pharmacokinetic parameters for both zolmitriptan and 183C91 and their 90% confidence intervals (CIs) were obtained and evaluated based on Sponsor's no-effect boundary of 0.5-2.0 pre-set for this study.

### *1.1. Recommendations*

Office of Clinical Pharmacology has reviewed the Phase 1 pharmacokinetic study (Study D1221C00004) 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

Section 3.1 of the review starting page 13. The Recommendations and labeling changes pertinent to the Clinical Pharmacology and Biopharmaceutics should be conveyed to the Sponsor.

### *1.2. Phase IV Commitments*

None

### *1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS*

The aim of the clinical pharmacology program was to demonstrate the pharmacokinetic differences of zolmitriptan in adolescents and adults after the intranasal dose. Pharmacokinetics of both zolmitriptan and its active metabolite, 183C91, were characterized in the Phase 1 pharmacokinetic study (D1221C0004) in both populations after a single 5-mg intranasal dose of zolmitriptan.

Pharmacokinetics of zolmitriptan in adolescents vs. adults:

- The systemic exposure measures (AUC0-∞, AUC0-t, and Cmax) of zolmotriptan following a single intranasal dose of 5-mg zolmitriptan were similar based on geometric mean ratios (adolescents had 8-13% lower AUCs and 3% lower Cmax compared to that seen in adults). However, we do not consider the no-effect boundary of 0.5-2.0 for the 90% CIs of the exposure measures, pre-set by the sponsor, to be valid and adequately justified.
- The clearance (CL/F) in adolescents was 15% higher than adults, corresponding to the slightly lower exposure.
- Female adolescents and adults had similar CL/F values (geometric mean ratio of 1.03), corresponding to the similar exposure between these two populations. However, male adolescents had an approximately 29% higher CL/F, on average, than adult male subjects, corresponding to approximately 22% lower exposure.
- The median Tmax was similar at about 2.0 hours in both adults and adolescents and t1/2 was slightly shorter at 3.0 hours in adolescents compared with 3.8 hours in adults.
- The median Tmax was 4.0 hours in female adolescents compared to 2.0 hours in female adults, although the ranges were similar.

Pharmacokinetics of 183C91 in adolescents vs. adults:

- The systemic exposure of the active metabolite was higher in adolescents than that seen in adults based on geometric mean ratios (adolescents had approximately 27-32% higher AUCs and 17% higher Cmax compared to adults).
- Male adolescents and adults had similar Cmax values, while female adolescents had an approximately 36% higher Cmax than female adults. The gender differences cannot be explained, as the male adolescents had lower exposure of parent compound to male adults, but with regards to the metabolite, the female adolescents had higher Cmax compared to female adults. The reason for this is not clear, based on the limited metabolic information.

- The Tmax was similar at approximately 4.0 hours in both adolescents and adults.
- The t1/2 was also similar in both groups at 3.4 and 3.8 hours for adolescents and adults, respectively.

Gender differences in adolescent pharmacokinetics:

- In adolescents, female subjects had approximately 28-35% higher zolmitriptan exposure (AUCs and Cmax) than that observed in male subjects, similar to that observed in adults and also described in approved label for oral tablets. These higher exposure in female adolescents corresponds to an approximately 28% lower CL/F.
- There are no significant gender differences for zolmitriptan with respect to the median Tmax (4.0 hours) or the t1/2 (3.2 hours for females and 3.6 hours for males).
- The gender differences for the active metabolite in AUCs were less pronounced than that for the parent drug. However, Cmax of the active metabolite was approximately 39% higher in female adolescents.

Ta-Chen Wu, 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 21-450 (S-005)
CSO/L. Chen
/ATL Clin Pharm/V. Tandon
/DDD Clin Pharm/R. Uppoor
HFD-860 /DD DCP-1/M. Mehta

## *2. QUESTION-BASED REVIEW (QBR)*

### *2.1. General Attributes of the Drug*

#### *2.1.1.* What pertinent regulatory background or history contributes to the current assessments of this drug?

Zomig® (zolmitriptan) was originally approved for oral tablet and orally disintegrating tablet of 2.5-mg and 5-mg strengths for the acute treatment of migraine with or without aura in adults (≥18 years of age). Zomig® (Zolmitriptan) Nasal Spray (NDA 21-450) was originally approved in the U.S. on 30 September 2003 for the same indication in adults.

On 14 December 2007, the sponsor submits a supplemental NDA for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12-17 years). The amended labeling includes changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use **(b) (4)** of the full prescribing information. However, the sponsor is not seeking an indication for the use of Zomig® (zolmitriptan) Nasal Spray for the acute treatment of migraine in adolescent population.

#### *2.1.2. What are the proposed mechanism of action and therapeutic indication?*

Zolmitriptan (a selective 5-HT $_{1B/1D}$ receptor agonist) and its N-desmethyl metabolite binds with high affinity to human recombinant 5 $HT_{1D}$ and 5 $HT_{1B}$ receptors while having modest affinity for 5-$HT_{1A}$ receptors. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5 $HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro inflammatory neuropeptide release.

ZOMIG Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults. ZOMIG is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of ZOMIG have not been established for cluster headache, which is present in an older, predominantly male population.

#### *2.1.3. What are the proposed dosages and route of administration?*

Zomig® Nasal Spray is supplied as an aqueous solution containing 50 mg/ml zolmitriptan and is delivered by the device in a 5 mg in a 100-µg unit dose aqueous buffered solution and is intended for a single intranasal use only.

## *2.2. General Clinical Pharmacology*

### *2.2.1. 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):

- Clinical Study Report for Pharmacokinetic Study D1221C00004
- Clinical Study Report for Efficacy Study D1221C00005
- Clinical Study Report for Safety Study 311CUS/0005 (previously submitted to NDA 20-768 on September 30, 2003)

Among these studies, the single dose pharmacokinetic study (D1221C0004) was designed to demonstrate the pharmacokinetic characteristics of zolmitripan after a nasal spray dose in adolescents as compared to that seen in adults. The 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 zolmitriptan. The design features of these pediatric clinical studies are shown in the table below.

Table 1. Tabular listing of the pediatric clinical studies

| Type of study/ Study identifier | Primary objective of the study | Study design and types of control | Test product; Dosage regimen; Route of admin. | Number of subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|---|---|---|---|---|---|---|
| PK study/ D1221C00004 | To compare pharmacokinetics of zolmitriptan 5 mg nasal spray in adolescent and adult migraineurs between migraine attacks | 2-center, open-label, nonrandomized, single-dose, parallel-group | A single dose of zolmitriptan 5 mg in a nasal spray device | 15 adults (≥18 years) and 15 adolescents (12 to 17 years, inclusive) | Adult and adolescent subjects with a history of migraine | Single dose |

| Type of study/ Study identifier | Primary objective of the study | Study design and types of control | Test product; Dosage regimen; Route of admin. | Number of subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|---|---|---|---|---|---|---|
| Efficacy and safety/ D1221C00005 | To evaluate the efficacy of zolmitriptan 5 mg nasal spray compared to placebo, for the acute treatment of migraine headache in adolescent subjects (aged 12 to 17 years) | Multicenter, double-blind, randomized, placebo-controlled, 2-way crossover study with a single-blind, placebo challenge (enriched population) | A single dose of zolmitriptan 5 mg/placebo in a commercial nasal spray device administered double-blind for two migraine headaches | 248 patients randomized; either zolmitriptan/ placebo (n=128) or placebo/zolmitriptan (n=120) | Migraine headache with or without aura (International Headache Society (IHS) and International Headache Society-Revised (IHS-R) criteria) | Single dose |

| | | | | | | |
|---|---|---|---|---|---|---|
| Safety and efficacy/ 311CUS/ 0005 | Phase I: To evaluate the efficacy of oral zolmitriptan across a range of doses for the treatment of a single migraine headache in adolescent patients (aged 12 to 17 years, inclusive) | A 2-phase, multicenter study<br>In Phase I, patients were randomized to treat a single migraine headache with either 2.5 mg, 5 mg, or 10 mg zolmitriptan, or placebo | In Phase I; a single oral dose of 2.5, 5, or 10 mg zolmitriptan or matching placebo | 850 patients randomised in Phase I were equally distributed among treatment groups: 2.5 mg (n=210) 5.0 mg (n=212) 10 mg (n=214) placebo (n=214) | Patients aged between 12 and 17 years (inclusive), with a minimum of 2 migraines per month (according to International Headache Society [IHS]-defined criteria) and a maximum of 10 migraine headaches or nonmigraine headaches each month | Single dose |
| | Phase II: To evaluate the safety of the long-term use of 5 mg oral zolmitriptan for the acute treatment of multiple migraine headaches in the same adolescents | In Phase II (open-label period) patients treated multiple migraine headaches over a 12-month period with 5 mg zolmitriptan (tablet form) | In Phase II; oral 5 mg zolmitriptan in an open-label fashion | 680 patients entered Phase II | | |

Study D1221C00004 was a 2-center, open label, nonrandomized, single-dose, parallel-group, Phase 1 study designed to establish pharmacokinetic differences between adolescent (12-17 years) and adult (≥18 years) populations following a single 5-mg dose of zolmitriptan nasal spray between migraine attacks. Approximately equal numbers of male and female subjects for each age group and approximately equal numbers of adolescents within the 2 age groups of 12-14 years and 15-17 years were recruited. The primary endpoint was $AUC_{inf}$ for zolmitriptan. The secondary endpoints included Cmax, AUC0-t, Tmax, t1/2 and CL/F. Similar pharmacokinetic parameters were also analyzed for the active metabolite 183C91 as secondary endpoints. There was no efficacy assessment in this study. Ratios of the geometric means (adolescent vs. adult) of pharmacokinetic parameters for both zolmitriptan and 183C91 and their 90% confidence intervals (CIs) were obtained and evaluated based on Sponsor's no-effect boundary of 0.5-2.0 pre-set for this study. There was no efficacy assessment in this study.

The efficacy trial (Study D1221C00004) was a multicenter, double-blind, randomized, placebo-controlled, 2-way crossover design with single placebo challenge (enrich population). Two co-primary endpoints were utilized to evaluate the efficacy results:

- 1-hour headache response (defined as an improvement in migraine headache intensity from severe or moderate to mild or none).
- 2-hour sustained headache response for those patients responding at 1 hour (defined as headache response at 1-hour post-randomized dose, without return to moderate or severe pain, and with no use of rescue medication through 2 hours).

The intent-to-treat (ITT) and the all randomized treated (ART) populations were analyzed as two different efficacy populations in this study.

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

The plasma levels of zolmitriptan and its active N-desmethyl metabolite (183C91) were identified and measured using validated bioanalytical methods employing validated high performance liquid chromatography-electrospray mass spectrometry (HPLC-MS/MS), as described in Individual Study Review (Section 4.2).

The active metabolite, 183C91, has high binding affinity for 5-$HT_{1B/1D}$ receptors (approximately 2-6 times compared with the parent drug) but has approximately 2/3 of the systemic exposure to the parent drug. Therefore, this active metabolite could have significant contribute to the overall activity following administration of Zomig.

### *2.2.3. What is the pharmacokinetics property of zolmitriptan and active metabolite (183C91) following a single intranasal dose of 5-mg Zomig nasal spray?*

The pharmacokinetics of zolmitriptan and its active metabolite, 183C91, were determined following a single intranasl dose of 5-mg zolmitriptan to adolesant and adult migraineurs in Study D1221C00004. The plasma samples for pharmacokinetic determination were collected up to 10 hours post-dose at specified time points.

Figures 1~3 shows the comparison of plasma concentrations of zolmitriptan and 183C91 for all adolescents and adults or respective gender following single intranasal doses of 5-mg zolmitriptan.

Figure 1. Mean plasma concentrations of zolmitriptan and 183C91 for all subjects

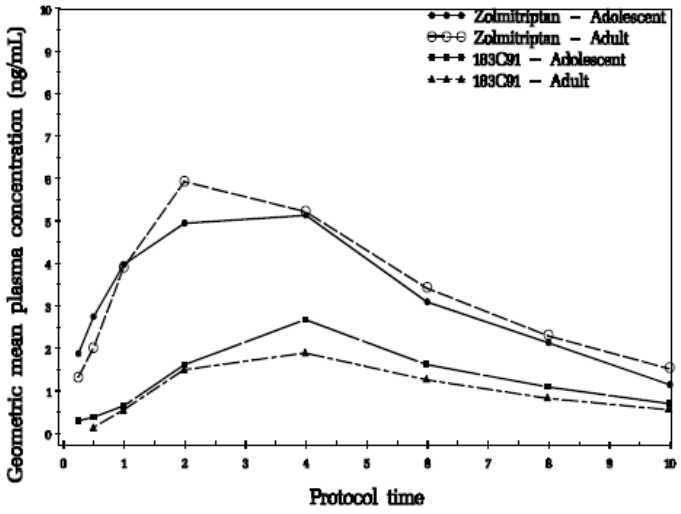


Figure 2. Geometric mean plasma concentrations for all male subjects

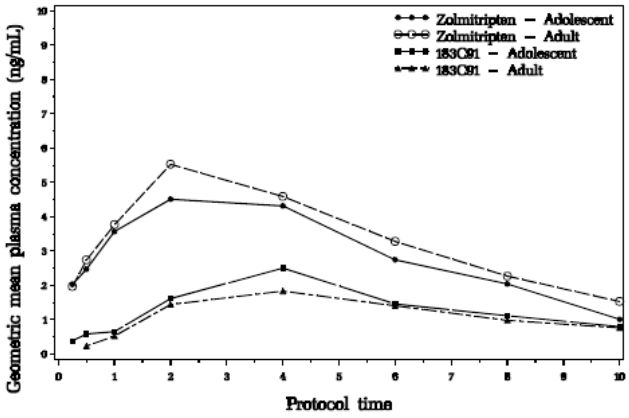
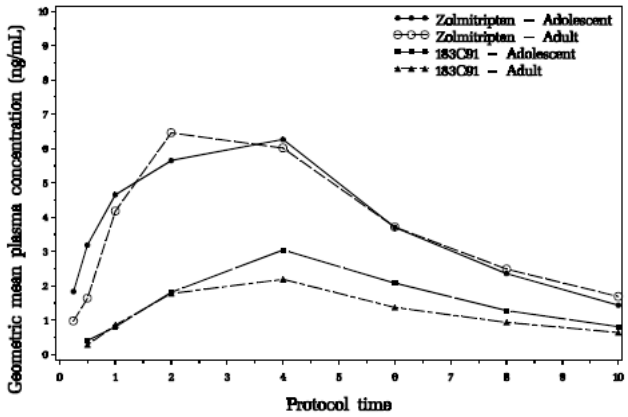



Figure 3. Geometric mean plasma concentrations for all female subjects




The summary of pharmacokinetic parameters for zolmitriptan and 183C91, and results of statistical analysis are shown in Table 2~3.

Table 2. Representative pharmacokinetic parameters for zolmitriptan and results of statistical analysis

| | | | **Adolescent** | | **Adult** | **Adolescent/Adult** |
|---|---|---|---|---|---|---|
| **Parameter** | **Gender** | **N** | **Geometric Means (95% CI range)** | **N** | **Geometric Means (95% CI range)** | **Geometric Mean Ratios (90% CI range)** |
| AUC (hr*ng/mL) | All | 15 | 40.9 (30.0, 55.6) | 15 | 46.9 (34.5, 63.9) | 0.87 (0.61, 1.25) |
| | Female | 7 | 48.2 (29.9, 77.9) | 8 | 49.5 (31.6, 77.4) | 0.98 (0.57, 1.67) |
| | Male | 8 | 34.9 (22.2, 54.9) | 7 | 44.9 (27.6, 72.9) | 0.78 (0.45, 1.34) |
| AUC(0-t) (hr*ng/mL) | All | 15 | 34.5 (25.4, 46.8) | 15 | 37.5 (27.7, 50.9) | 0.92 (0.64, 1.32) |
| | Female | 7 | 41.6 (26.3, 65.7) | 8 | 40.4 (26.3, 62.0) | 1.03 (0.62. 1.72) |
| | Male | 8 | 28.8 (18.2, 45.7) | 7 | 35.1 (21.5, 57.5) | 0.82 (0.47, 1.43) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cmax (ng/mL) | All | 15 | 6.2 (4.7, 8.2) | 15 | 6.4 (4.9, 8.5) | 0.97 (0.70, 1.34) |
| | Female | 7 | 7.7 (5.2, 11.5) | 8 | 7.1 (4.9, 10.3) | 1.09 (0.69, 1.71) |
| | Male | 8 | 5.0 (3.3, 7.7) | 7 | 5.9 (3.7, 9.3) | 0.86 (0.51, 1.43) |
| CL/F (L/h) | All | 15 | 122.4 (89.9, 166.7) | 15 | 106.5 (78.2, 145.0) | 1.15 (0.80, 1.65) |
| | Female | 7 | 103.6 (64.2, 167.3) | 8 | 101.0 (64.6, 158.1) | 1.03 (0.6, 1.76) |
| | Male | 8 | 143.4 (91.2, 225.7) | 7 | 111.4 (68.6, 180.9) | 1.29 (0.75, 2.22) |
| | **Gender** | **N** | **Arithmetic mean or median (range)** | **N** | **Arithmetic mean or median (range)** | |
| Tmax [a] (hours) | All | 15 | 2.0 (0.3, 4.0) | 15 | 2.0 (1.0, 4.0) | |
| | Female | 7 | 4.0 (0.50, 4.0) | 8 | 2.0 (1.0, 4.0) | |
| | Male | 8 | 2.0 (0.3, 4.0) | 7 | 2.0 (1.0, 4.0) | |
| t1/2 [a] (hours) | All | 15 | 3.0 (1.0, 4.8) | 15 | 3.8 (2.2, 5.5) | |
| | Female | 7 | 3.0 (2.2, 3.8) | 8 | 3.5 (2.2, 5.2) | |
| | Male | 8 | 3.0 (1.0, 4.8) | 7 | 4.1 (2.7, 5.5) | |

a. Arithmetic mean for t1/2; median for Tmax

Table 3. Representative pharmacokinetic parameters for 183C91 and results of statistical analysis

| | | | **Adolescent** | | **Adult** | **Adolescent/Adult** |
|---|---|---|---|---|---|---|
| **Parameter** | **Gender** | **N** | **Geometric Means (95% CI range)** | **N** | **Geometric Means (95% CI range)** | **Geometric Mean Ratios (90% CI range)** |
| AUC (hr*ng/mL) | All | 13 | 20.4 (15.8, 26.5) | 15 | 16.1 (12.7, 20.5) | 1.27 (0.94, 1.70) |
| | Female | 7 | 21.7 (14.9, 31.6) | 8 | 16.4 (11.6, 23.4) | 1.32 (0.86, 2.01) |
| | Male | 6 | 19.2 (12.6, 29.1) | 7 | 15.8 (10.8, 23.3) | 1.21 (0.76, 1.92) |
| AUC(0-t) (hr*ng/mL) | All | 13 | 16.2 (12.4, 21.2) | 15 | 12.3 (9.6, 15.8) | 1.32 (0.97, 1.78) |
| | Female | 7 | 17.7 (11.9, 26.2) | 8 | 12.9 (8.9, 18.7) | 1.37 (0.88, 2.13) |
| | Male | 6 | 14.7 (9.6, 22.6) | 7 | 11.7 (7.9, 17.4) | 1.26 (0.78, 2.02) |
| Cmax (ng/mL) | All | 15 | 2.4 (1.7, 3.4) | 15 | 2.1 (1.5, 2.9) | 1.17 (0.79, 1.72) |
| | Female | 7 | 3.1 (2.0, 4.7) | 8 | 2.3 (1.5, 3.4) | 1.36 (0.84, 2.18) |
| | Male | 8 | 1.9 (1.1, 3.4) | 7 | 1.9 (1.1, 3.5) | 1.01 (0.52, 1.94) |
| | **Gender** | **N** | **Arithmetic mean or median (range)** | **N** | **Arithmetic mean or median (range)** | |
| Tmax [a] (hours) | All | 15 | 4.0 (2.0, 6.0) | 15 | 4.0 (2.0, 6.0) | |
| | Female | 7 | 4.0 (2.0, 4.0) | 8 | 4.0 (2.0, 4.0) | |
| | Male | 8 | 4.0 (4.0, 6.0) | 7 | 4.0 (2.0, 6.0) | |
| t1/2 [a] (hours) | All | 13 | 3.4 (2.3, 5.7) | 15 | 3.8 (2.0, 5.9) | |
| | Female | 7 | 3.2 (2.3, 5.7) | 8 | 3.7 (2.0, 5.9) | |

| | | | | |
|---|---|---|---|---|
| Male | 6 | 3.6 (2.6, 4.7) | 7 | 3.9 (2.6, 5.2) |

a. Arithmetic mean for t1/2; median for Tmax

### *2.2.4. Are there significant differences in zolmitriptan pharmacokinetics between adolescents and adults?*

As shown in Table 2:

- The systemic exposure measures (AUC0-∞, AUC0-t, and Cmax) of zolmotriptan following a single intranasal dose of 5-mg zolmitriptan were similar based on geometric mean ratios (adolescents had 8-13% lower AUCs and 3% lower Cmax compared to that seen in adults). However, we do not consider the no-effect boundary of 0.5-2.0 for the 90% CIs of the exposure measures, pre-set by the sponsor, to be valid and adequately justified.
- The clearance (CL/F) in adolescents (122.4 L/h) was 15% higher than adults, corresponding to the slightly lower exposure.
- Female adolescents and adults had similar CL/F values (geometric mean ratio of 1.03), corresponding to the similar exposure between these two populations. However, male adolescents had an approximately 29% higher CL/F, on average, than adult male subjects, corresponding to approximately 22% lower exposure.
- The median Tmax was similar at about 2.0 hours in both adults and adolescents and t1/2 was slightly shorter at 3.0 hours in adolescents compared with 3.8 hours in adults.
- The median Tmax was 4.0 hours in female adolescents compared to 2.0 hours in female adults, although the ranges were similar.

### *2.2.5. Are there any significant differences in zolmitriptan pharmacokinetics between adolescents?*

- In adolescents, female subjects had approximately 28-35% higher zolmitriptan exposure (AUCs and Cmax) than that observed in male subjects, similar to that observed in adults and also described in approved label for oral tablets. These higher exposure in female adolescents corresponds to an approximately 28% lower CL/F.
- There are no significant gender differences for zolmitriptan with respect to the median Tmax (4.0 hours) or the t1/2 (3.2 hours for females and 3.6 hours for males).
- The gender differences for the active metabolite in AUCs were less pronounced than that for the parent drug. However, Cmax of the active metabolite was approximately 39% higher in female adolescents.

### *2.2.6. Are there significant differences in 183C91 between adolescents and adults?*

As shown in Table 3:

- The systemic exposure of the active metabolite was higher in adolescents than that seen in adults based on geometric mean ratios (adolescents had approximately 27-32% higher AUCs and 17% higher Cmax compared to adults).

- Male adolescents and adults had similar Cmax values, while female adolescents had an approximately 36% higher in Cmax than female adults. The gender differences cannot be explained, as the male adolescents had lower exposure of parent compound to male adults, but with regards to the metabolite, the female adolescents had higher Cmax compared to female adults. The reason for this is not clear, based on the limited metabolic information.
- The Tmax was similar at approximately 4.0 hours in both adolescents and adults.
- The t1/2 was also similar in both groups at 3.4 and 3.8 hours for adolescents and adults, respectively.

## 3. DETAILED LABELING RECOMMENDATION

The OCP has not made recommendation (see track changes with yellow highlight below) for the proposed language addition to the approved label for Zomig® (Zolmitriptan) Nasal Spray. The proposed changes are in yellow highlight: the <u>underlined text</u> is the proposed change to the label language; the ~~strikethrough~~ is recommendation for deletion from the perspective of OCP.

<u>Labeling</u> recommendation to be sent to the Sponsor:

1. (b) (4)

### 3.1. Proposed Package Insert



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

## 4. APPENDICES

### *4.1 Clinical Pharmacology and Biopharmaceutics Individual Study Review*

**Study D1221C00004:** "Open Label, Nonrandomized Comparison of the Pharmacokinetics of a Single 5.0-mg Dose of Zolmitriptan in Adult and Adolescent Migraineurs when Given as a Nasal Spray Between Migraine Attacks"

**Principal Investigator/Coordinating Investigator:**

- Paul Winner, DO, Premier Research Institute at Palm Beach Neurology, West Palm Beach, Florida.
- Stephen Linder, MD, Dallas Pediatric Neurology Associates, Dallas, Texas.

**Study Period:** 20 February 2003 – 13 April 2003

**Study Drug:**

- Zolmitriptan 5.0 mg nasal spray: Formulation (F) number, F12441; Batch (B) number, BC612
- Placebo for zolmitriptan 5.0 mg nasal spray: F number, F12787; B number, AY279

**Objectives:**
Primary: To compare the pharmacokinetics of zolmitriptan 5.0 mg nasal spray in adolescent migraineurs with that in adult migraineurs between migraine attacks
Secondary: To collect safety and tolerability data on zolmitriptan 5.0 mg nasal spray in adolescents and adults.

**Study Design:**
This was a 2-center, open label, nonrandomized, single-dose, parallel-group, Phase 1 study in adult aged ≥18 years and adolescent subjects aged 12-17 years, inclusive, with a history of migraine. A total of 15 adults (male and female) and 15 adolescents (male and female) who met all screening criteria were enrolled in the study in order to obtain 12 evaluable adults and 12 evaluable adolescents. The sponsor recruited approximately equal numbers of male and female subjects for each age group and approximately equal numbers of adolescents within the 2 age groups of 12 to 14 years and 15 to 17 years.

While between migraine attacks, adult and adolescent subjects returned to the investigation site within a minimum of 5 days and a maximum of 28 days from the screening visit to receive a single 5.0 mg dose of zolmitriptan administered as a nasal spray. The PK plasma samples for assay of zolmitriptan and 183C91 were obtained at pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 10.0 hours post-dose. A one-day follow-up visit and a follow-up phone call occurred within 24 hours and 7 days after treatment, respectively. There was no efficacy assessment in this study.

Pharmacokinetics Assessments:

- Primary PK endpoint: AUC0-∞ for zolmitriptan

- Secondary PK endpoints: Cmax, AUC0-t, Tmax, t1/2, and CL/F of zolmitriptan
- The AUC and the same secondary PK parameters, except CL/F, were also calculated for the active metabolite 183C91.

Safety Assessments: monitoring of adverse events (AEs) (including nasopharyngeal AEs), physical examinations (including nasopharyngeal examinations), vital signs measurements, clinical laboratory testing, and 12-lead ECGs.

Statistical Analysis:
Log-transformed AUC and Cmax for both zolmitriptan and 183C91, and log-transformed clearance for zolmitriptan were analyzed using an ANOVA model with respect to age group and gender. The least square (LS) means, the difference in LS means, and corresponding 95% CIs between adolescents and adults. The ratios of the geometric means (adolescent vs. adult) of exposure measures and their 90% CIs were calculated, with a pre-set no-effect boundary of 90% CI of 0.5-2.0 for AUC and Cmax to conclude a lack of PK difference and clinical significance. The remaining secondary endpoints were not formally analyzed, but summary statistics were provided for the results and the remaining secondary endpoints.

**Summary of Analytical Reports:**
The plasma samples were stored frozen at approximately –20 ± 10°C until assayed at the **(b) (4)**
Plasma samples for measurement of zolmitriptan and 183C91 concentrations were analyzed by a validated high performance liquid chromatography-electrospray mass spectrometry (HPLC-MS/MS) method. Human plasma was used for preparing analytical runs, calibration, and quality control samples. The limit of quantification (LOQ) was 0.1 ng/ml for zolmitriptan and 0.2 ng/ml for the metabolite, 183C91. The calibration range was 0.100-15.0 ng/ml for zolmitriptan and 0.200-15.0 ng/ml for 183C91.

Assay validation and quality control for Study D1221C00004 are summarized in the following Tables:

| | | | **Zolmitriptan** | **183C91** |
|---|---|---|---|---|
| **Method:** | | | HPLC-MS/MS | HPLC-MS/MS |
| **Standard Curve** | Range: | | 0.100-15.0 ng/ml (0.100, 0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 15.0 ng/ml) | 0.200-15.0 ng/ml (0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 15.0 ng/ml) |
| | | Precision: | 1.9 - 7.5 % | 1.2 – 7.1 % |
| | | Accuracy: | -4.8 - 5.9 % | -6.4 – 5.5 % |
| | Linearity: | | r = 0.9974 | r = 0.9974 |
| **LOQ** | LLOQ: | | 0.1 ng/ml | 0.2 ng/ml |
| **QC** | Low: | | 0.300 ng/ml | 0.600 ng/ml |
| | | Precision: | 16.5 % | 13.7 % |
| | | Accuracy: | 0.5 % | -6.7 % |
| | Med: | | 5.00 ng/ml | 5.00 ng/ml |
| | | Precision: | 7.7 % | 9.4 % |
| | | Accuracy: | 2.8 % | 4.1 % |
| | High: | | 12.0 ng/ml | 12.0 ng/ml |
| | | Precision: | 5.4 % | 6.6 % |
| | | Accuracy: | 8.8 % | -1.7 % |

The bioanalytical method for determining the zolmitriptan and 183C91 plasma concentrations for PK characterization is found to be adequate and acceptable from a clinical pharmacology perspective.

**RESULTS:**

**Demographics:**
A total of 30 subjects (15 adolescents and 15 adults) participated in the study, received study treatment, and completed the study. The mean age of subjects was 14.4 (12-17) years and 39.1 (19-63) years for adolescents and adults, respectively. All 30 subjects were included in the PK and safety analyses. Terminal slopes of the plasma versus time curve of 183C91 for Subjects 201 and 204 could not be estimated. Demographic and baseline characteristics of the subjects who received treatment are shown in the Table 1 below:

Table 1: Demographic and baseline characteristics

| Demographic or baseline characteristic | | Age group | |
|---|---|---|---|
| | | Adolescents N=15 | Adults N=15 |
| **Demographic characteristics** | | | |
| Sex n and (%) of subjects | Male | 8 (53.3) | 7 (46.7) |
| | Female | 7 (46.7) | 8 (53.3) |
| Race-Ethnicity, n and (%) of subjects | Caucasian | 13 (86.7) | 9 (60.0) |
| | Black | 0 | 1 (6.7) |
| | Hispanic | 2 (13.3) | 5 (33.3) |
| **Baseline characteristics** | | | |
| Age (years) | Mean (SD) | 14.4 (1.6) | 39.1 (13.6) |
| | Median | 14 | 37 |
| | Range | 12 to 17 | 19 to 63 |
| Weight (kg) | Mean (SD) | 53.9 (9.7) | 78.9 (19.8) |
| | Median | 53.0 | 74.0 |
| | Range | 37 to 69 | 46 to 109 |
| Height (cm) | Mean (SD) | 163 (11) | 168 (10) |
| | Median | 158 | 167 |
| | Range | 145 to 179 | 151 to 182 |
| BMI ($kg/m^2$) | Mean (SD) | 20.3 (2.9) | 27.5 (5.2) |
| | Median | 19.7 | 27.8 |
| | Range | 14.8 to 27.6 | 19.1 to 35.3 |

**Pharmacokinetics Results:**
The mean plasma concentration-time profiles of zolmitriptan and the active metabolite, 183C91 for all adolescents and adults or respective gender following single intranasal doses of 5-mg zolmitriptan are shown in Figures 1~3 below.

Figure 1. Geometric mean plasma concentrations for all subjects

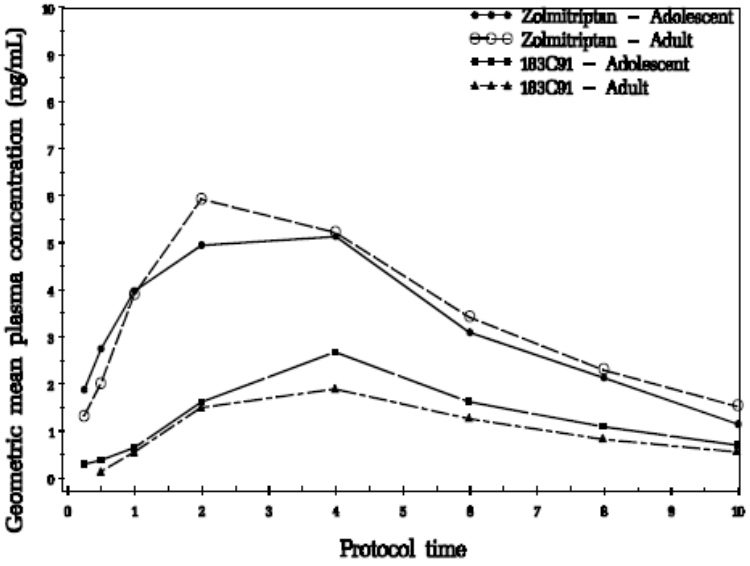



Figure 2. Geometric mean plasma concentrations for all male subjects

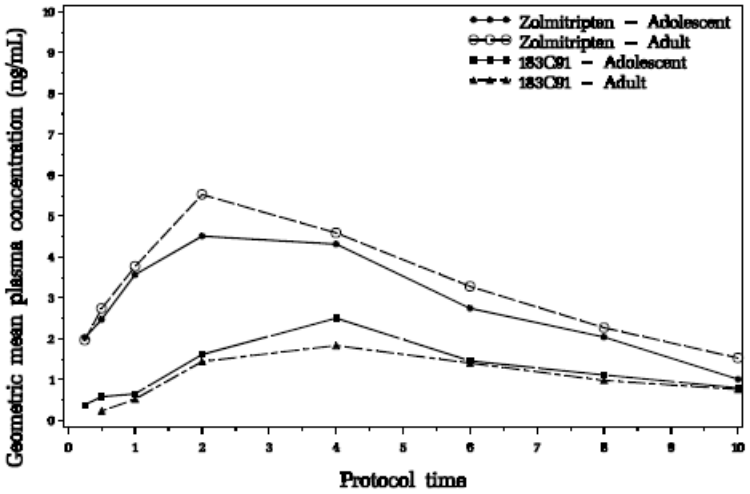
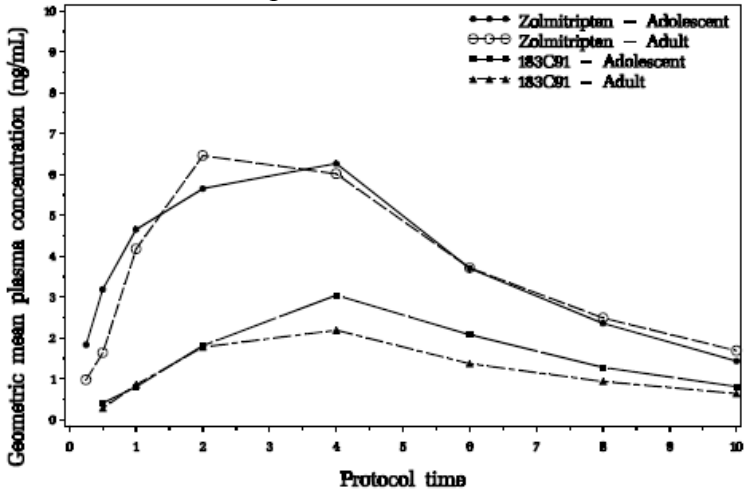



Figure 3. Geometric mean plasma concentrations for all female subjects



The summary of pharmacokinetic parameters for zolmitriptan and results of statistical analysis are shown in Table 2.

Table 2. Representative PK parameters for zolmitriptan and results of statistical analysis

| | | | Adolescent | | Adult | Adolescent/Adult |
|---|---|---|---|---|---|---|
| **Parameter** | **Gender** | **N** | **Geometric Means (95% CI range)** | **N** | **Geometric Means (95% CI range)** | **Geometric Mean Ratios (90% CI range)** |
| AUC (hr*ng/mL) | All | 15 | 40.9 (30.0, 55.6) | 15 | 46.9 (34.5, 63.9) | 0.87 (0.61, 1.25) |
| | Female | 7 | 48.2 (29.9, 77.9) | 8 | 49.5 (31.6, 77.4) | 0.98 (0.57, 1.67) |
| | Male | 8 | 34.9 (22.2, 54.9) | 7 | 44.9 (27.6, 72.9) | 0.78 (0.45, 1.34) |
| AUC(0-t) (hr*ng/mL) | All | 15 | 34.5 (25.4, 46.8) | 15 | 37.5 (27.7, 50.9) | 0.92 (0.64, 1.32) |
| | Female | 7 | 41.6 (26.3, 65.7) | 8 | 40.4 (26.3, 62.0) | 1.03 (0.62. 1.72) |
| | Male | 8 | 28.8 (18.2, 45.7) | 7 | 35.1 (21.5, 57.5) | 0.82 (0.47, 1.43) |
| Cmax (ng/mL) | All | 15 | 6.2 (4.7, 8.2) | 15 | 6.4 (4.9, 8.5) | 0.97 (0.70, 1.34) |
| | Female | 7 | 7.7 (5.2, 11.5) | 8 | 7.1 (4.9, 10.3) | 1.09 (0.69, 1.71) |
| | Male | 8 | 5.0 (3.3, 7.7) | 7 | 5.9 (3.7, 9.3) | 0.86 (0.51, 1.43) |
| CL/F (L/h) | All | 15 | 122.4 (89.9, 166.7) | 15 | 106.5 (78.2, 145.0) | 1.15 (0.80, 1.65) |
| | Female | 7 | 103.6 (64.2, 167.3) | 8 | 101.0 (64.6, 158.1) | 1.03 (0.6, 1.76) |
| | Male | 8 | 143.4 (91.2, 225.7) | 7 | 111.4 (68.6, 180.9) | 1.29 (0.75, 2.22) |
| | **Gender** | **N** | **Arithmetic mean or median (range)** | **N** | **Arithmetic mean or median (range)** | |
| Tmax [a] (hours) | All | 15 | 2.0 (0.3, 4.0) | 15 | 2.0 (1.0, 4.0) | |
| | Female | 7 | 4.0 (0.50, 4.0) | 8 | 2.0 (1.0, 4.0) | |
| | Male | 8 | 2.0 (0.3, 4.0) | 7 | 2.0 (1.0, 4.0) | |
| t1/2 [a] (hours) | All | 15 | 3.0 (1.0, 4.8) | 15 | 3.8 (2.2, 5.5) | |
| | Female | 7 | 3.0 (2.2, 3.8) | 8 | 3.5 (2.2, 5.2) | |
| | Male | 8 | 3.0 (1.0, 4.8) | 7 | 4.1 (2.7, 5.5) | |

a. Arithmetic mean for t1/2; median for Tmax

The summary of pharmacokinetic parameters for 183C91 and results of statistical analysis are shown in Table 3. The terminal slope of the plasma concentration-time curve of 183C91 for Subjects 201 and 204 could not be estimated due to the limitation of quantification, which resulted in some missing valued included in data analysis, as seen in the table.

Table 3. Representative PK parameters for 183C91 and results of statistical analysis

| | | | Adolescent | | Adult | Adolescent/Adult |
|---|---|---|---|---|---|---|
| **Parameter** | **Gender** | **N** | **Geometric Means (95% CI range)** | **N** | **Geometric Means (95% CI range)** | **Geometric Mean Ratios (90% CI range)** |
| AUC (hr*ng/mL) | All | 13 | 20.4 (15.8, 26.5) | 15 | 16.1 (12.7, 20.5) | 1.27 (0.94, 1.70) |
| | Female | 7 | 21.7 (14.9, 31.6) | 8 | 16.4 (11.6, 23.4) | 1.32 (0.86, 2.01) |
| | Male | 6 | 19.2 (12.6, 29.1) | 7 | 15.8 (10.8, 23.3) | 1.21 (0.76, 1.92) |
| AUC(0-t) (hr*ng/mL) | All | 13 | 16.2 (12.4, 21.2) | 15 | 12.3 (9.6, 15.8) | 1.32 (0.97, 1.78) |
| | Female | 7 | 17.7 (11.9, 26.2) | 8 | 12.9 (8.9, 18.7) | 1.37 (0.88, 2.13) |
| | Male | 6 | 14.7 (9.6, 22.6) | 7 | 11.7 (7.9, 17.4) | 1.26 (0.78, 2.02) |
| Cmax (ng/mL) | All | 15 | 2.4 (1.7, 3.4) | 15 | 2.1 (1.5, 2.9) | 1.17 (0.79, 1.72) |
| | Female | 7 | 3.1 (2.0, 4.7) | 8 | 2.3 (1.5, 3.4) | 1.36 (0.84, 2.18) |
| | Male | 8 | 1.9 (1.1, 3.4) | 7 | 1.9 (1.1, 3.5) | 1.01 (0.52, 1.94) |
| | **Gender** | **N** | **Arithmetic mean or median (range)** | **N** | **Arithmetic mean or median (range)** | |
| Tmax [a] (hours) | All | 15 | 4.0 (2.0, 6.0) | 15 | 4.0 (2.0, 6.0) | |
| | Female | 7 | 4.0 (2.0, 4.0) | 8 | 4.0 (2.0, 4.0) | |
| | Male | 8 | 4.0 (4.0, 6.0) | 7 | 4.0 (2.0, 6.0) | |
| t1/2 [a] (hours) | All | 13 | 3.4 (2.3, 5.7) | 15 | 3.8 (2.0, 5.9) | |
| | Female | 7 | 3.2 (2.3, 5.7) | 8 | 3.7 (2.0, 5.9) | |
| | Male | 6 | 3.6 (2.6, 4.7) | 7 | 3.9 (2.6, 5.2) | |

a. Arithmetic mean for t1/2; median for Tmax

Safety:

No deaths or withdrawals occurred during the study. The only serious AE of hyperanticoagulation (anticoagulant effect increased) was assessed by the investigator as not related to treatment. Dysgeusia was the most commonly reported AE in both treatment groups and was considered by the investigators as possibly treatment-related in all cases. Nasal and pharyngeal AEs typical of triptan administration occurred in 3 adolescents and 6 adults. The majority of all AEs were mild in intensity. No clinically important abnormalities were observed during the study. Most AEs were mild in intensity. Only 1 chemistry abnormality of hyperkalemia was considered an AE that was potentially treatment related but could have been possibly caused by sample hemolysis.

Similar proportion of subjects with adverse events by category and the number of events were reported between adolescents and adults. Summary of AEs is shown in Tables 4~5.

Table 4. Number (%) of subjects who had an AE in any category

| Category of adverse event | Number (%) of subjects who had an adverse event in each category[a, b] | | | | | |
|---|---|---|---|---|---|---|
| | Adolescents N=15 | | | Adults N=15 | | |
| | n | % | No. of Events | n | % | No. of Events |
| Any adverse events | 14 | 93.3 | 32 | 13 | 86.7 | 31 |
| Nasopharyngeal adverse events | 3 | 20.0 | 4 | 6 | 40.0 | 7 |
| Serious adverse events | 0 | 0 | 0 | 1 | 6.7 | 1 |
| Serious adverse events leading to death | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinuations of study treatment due to adverse events | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment-related adverse events | 12 | 80.0 | 25 | 13 | 86.7 | 26 |

Table 5. Number (%) of subjects with the most commonly reported AEs

| Preferred term | Adolescents (N=15) | | Adults (N=15) | |
|---|---|---|---|---|
| | n | %[a] | n | %[a] |
| Dysgeusia | 12 | 80.0 | 9 | 60.0 |
| Headache | 3 | 20.0 | 3 | 20.0 |
| Dizziness | 2 | 13.3 | 2 | 13.3 |
| Rhinorrhoea | 1 | 6.7 | 2 | 13.3 |
| Pharyngolaryngeal pain | 0 | 0 | 3 | 20.0 |
| Dry mouth | 0 | 0 | 2 | 13.3 |

**CONCLUSIONS:**

1. For the parent drug, zolmitriptan:
   - The sponsor reported that adolescents had similar exposure when compared with adults based on the geometric mean ratios of AUC, AUC0-t, and Cmax, using a no-effect boundary of 90% CIs of 0.5-2.0 (to conclude that no clinically relevant differences).
   - The level of zolmitriptan exposure was similar between female adolescents and adults. However, male adolescents had a slightly lower AUC compared with male adults.
   - In adolescents, female subjects had higher zolmitriptan exposure (AUC and Cmax) then that observed in male subjects.
   - The sponsor did not consider the slight difference to be clinically meaningful.
   - Female adolescents and adults had similar CL/F values (geometric mean ratio of 1.03), while male adolescents had a slightly higher CL/F with a ratio of 1.29.
   - The median Tmax was similar at about 2.0 hours in both adults and adolescent and t1/2 was slightly shorter at 3.0 hours in adolescents compared with 3.8 hours

in adults. The median Tmax was 4.0 hours in female adolescents compared to 2.0 hours in female adults.

2. For the metabolite, 183C91:
   - Adolescents had a slightly higher exposure (~30% on average) when compared with adults based on the geometric mean ratios of AUC and AUC0-t, irrespective of gender.
   - Adolescents had a slightly higher Cmax (~17% on average) when compared with adults. While male adolescents and adults had similar Cmax values, female adolescents had a slightly higher Cmax than female adults with a ratio of 1.36.
   - The Tmax was similar at approximately 4.0 hours in both adolescents and adults.
   - The t1/2 was also similar in both groups at 3.4 and 3.8 hours for adolescents and adults, respectively.

3. The single intranasal dose of 5-mg zolmitriptan was reported to be well tolerated in adolescents and adults without safety concerns.

Reviewer's comments:

- The Agency recommends the use of 90% confidence interval of 80-125% (or 0.8-1.25) as acceptance criteria to demonstrate the bioequivalence or the similarity of the PK profiles. Strictly based on this BE acceptance criteria, it appears that the exposure measures of both the parent drug, zolmitriptan, and its active metabolite following a single intranasal dose of 5-mg zolmitriptan in adolescents are not considered "bioequivalent" to those obtained from the adults.
- While the exposure of zolmitriptan seems to be similar based on geometric mean ratios, the exposure of its active metabolite (183C91) was approximately 17~30% higher in adolescents.

We do not consider the no-effect boundary of 0.5-2.0 for the 90% CIs of the exposure measures, pre-set by the sponsor, to be valid and adequately justified for this indication. Therefore, the final decision will likely rely on the clinical judgment on the basis of efficacy and safety results.

## *4.2 Cover Sheet and OCPB Filing/Review Form*

*Office of Clinical Pharmacology and Biopharmaceutics*

*New Drug Application Filing and Review Form*

### General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **21-450 (S-005)** | **Brand Name** | **ZOMIG® (zolmitriptan) Nasal Spray** |
| **OCPB Division (I, II, III)** | **DCP-I** | **Generic Name** | **Zolmitriptan** |
| **Medical Division** | **HFD-120** | **Drug Class** | **Triptan** |
| **OCPB Reviewer** | **Ta-Chen Wu, PhD** | **Indication(s)** | **Acute treatment of migraine with or without aura in adults** |
| **OCPB Team Leader** | **Ramana S. Uppoor, PhD** | **Dosage Form** | **Nasal Spray (5 mg)** |
| | | **Dosing Regimen** | **Single 5 mg dose; may repeat after 2 hours if needed; not to exceed 10 mg in any 24 hour period.** |
| **Date of Submission** | **December 14, 2007** | **Route of Administration** | **Intranasal** |
| **Estimated Due Date of OCPB Review** | **8/26/08** | **Sponsor** | **AstraZeneca Pharmaceuticals LP** |
| **PDUFA Due Date** | **10/14/08** | **Priority Classification** | **S** |
| **Division Due Date** | **9/12/08** | | |

### Clin. Pharm. And Biopharm. Information

**Summary:**

ZOMIG® (Zolmitriptan) Nasal Spray (NDA 21-450; **(b) (4)** 5-mg strengths) was originally approved for the acute treatment of migraine with or without aura in adults (≥18 years of age). The sponsor submits a sNDA for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12-17 years). The amended labeling involves changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use and CLINICAL PHARMACOLOGY, Pharmacokinetics section of the full prescribing information. However, considering the Agency's concerns with respect to the drafting of appropriate language for inclusion in the DOSAGE and ADMINISTRATION of the full prescribing information, the sponsor is not seeking an indication for the use of ZOMIG® (zolmitriptan) Nasal Spray for the acute treatment of migraine in adolescents.

The following pediatric clinical study reports are submitted to fulfill the required pediatric study commitments:
• Clinical Study Report for Pharmacokinetic Study D1221C00004
• Clinical Study Report for Efficacy Study D1221C00005
• Clinical Study Report for Safety Study 311CUS/0005 (previously submitted to NDA 20-768 on September 30, 2003)

Study D1221C00004: This Phase 1 study was designed and conducted to establish that there are no PK differences between adolescent and adult populations following a single 5-mg dose of zolmitriptan nasal spray between migraine attacks. The primary endpoint was $AUC_{inf}$ for zolmitriptan. The secondary endpoints included Cmax, AUCt, Tmax, t1/2 and CL/F. Similar PK parameters were also analyzed for the active metabolite 183C91. There was no efficacy assessment in this study. Ratios of the geometric means (adolescent vs. adult) of PK parameters for both zolmitriptan and 183C91 and their 90% CIs were obtained.

| | "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** | | | "Overview of Clinical Pharmacology" as part of the "Clinical Overview" |
| **Labeling** | **X** | | | Annotated and non-annotated PDF files; Non-annotated Word file |
| **Reference Bioanalytical and Analytical Methods** | **X** | | | Pre-study validation report is not provided |
| **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: | **X** | **1** | **-** | Study D1221C00004 (PK) |
| 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** | **-** | 3 submitted (only 1 for PK):<br>Study D1221C00004 (PK)<br>Study D1221C00005 (Efficacy)<br>Study 311CUS/0005 (Safety) |
| 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** | **11** | **-** | |
| **Total Number of Studies** | | **1** | **1** | |
| | | | | |

**Filability and QBR comments**

| | **"X" if yes** | **Comments** |
|---|---|---|
| **Application filable ?** | **X** | Reasons if the application is not filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | **X** | Comments have been sent to firm (or attachment included). FDA letter date if applicable.<br>Please forward to Sponsor:<br><br>1. Please provide the validation report pertinent to the bioanalytical method used for the Pharmacokinetic Study D1221C00004.<br><br>2. Please provide electronic datasets for individual plasma concentrations and PK parameters used for PK analyses as SAS transport files (.XPT) for Study D1221C00004.<br><br>3. For Study D1221C00004, please provide the basis or justification for selecting the no-effect boundary of 90% CIs of 0.5-2.0 for AUC and Cmax to conclude a lack of PK differences and clinical significance between adult and adolescent migraineurs. |
| **QBR questions (key issues to be considered)** | • Adequate PK assessments for zolmitriptan nasal spray, and PK comparison in adolescent vs. adult migraineurs<br>• Adequately and appropriately validated bioanalytical methods | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | | |
| **Secondary reviewer Signature and Date** | | |

**CC: NDA 21-450, HFD-850(Electronic Entry or Lee), HFD-120(L. Chen), HFD-860 (R. Uppoor, M. Mehta)**

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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.**

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/s/
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Ta-Chen Wu
10/6/2008 02:34:39 PM
BIOPHARMACEUTICS

Veneeta Tandon
10/6/2008 02:41:28 PM
BIOPHARMACEUTICS