Clinical Review Cover Sheet
Pediatric Exclusivity Determination Review

NDA:	**20-768 (Sequence 012)**
Sponsor:	**Astra Zeneca**
Document Type	(b) (4)
Drug:	**Zomig Tablet (zolmitriptan)**
Proposed Indication:	**Migraine (adolescent)**
Correspondence Date:	**September 30, 2003**
Date Review Completed:	**December 2, 2003**
Date of Exclusivity Board	**December 8, 2003**
Division:	**Division of Neuropharmacological Drug Products (HFD-120)**
Reviewer:	**Kevin Prohaska, D.O.**

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Clinical Review for NDA 20-768 (b) (4)

1. Introduction and Background

AstraZeneca submits a Pediatric Exclusivity Submission in accordance with Section 111 of Title 1 of the Food and Drug Administration Act [Section 505A of the Federal Food, Drug, and Cosmetic Act]. The sponsor seeks Agency approval of their proposed labeling changes and requests six-month pediatric exclusivity for completing all required studies as outlined in the original Pediatric Written request (March 26, 1999) and amended on May 29, 2002 (date extension only).

The purpose of this review is for preparation of the upcoming Pediatric Exclusivity Board Meeting. The format of this review will include the recommended tabular summary of the specific details required in the Pediatric Written request as well as the sponsor's response. A brief description of the design and outcome of each trial as well as my commentary will follow the tabular summary. A biopharmacology consult has been requested to assess the adequacy of the sponsor's pharmacokinetic studies. A statistical consult has been requested to evaluate the adequacy of the data analyses. A complete review of the submission as well as a complete labeling review will be done in a separate document.

In the Pediatric Written Request (WR) we requested the sponsor conduct the following 4 clinical trials: an inpatient adolescent safety study if doses >5mg are proposed (study 1), a study to compare the PK of Zomig Tablet in adults and adolescents with a history of migraine (study 2), an acute safety and efficacy trial in adolescents (study 3), and a long term safety study in adolescents (study 4). In response the sponsor submits the results of 6 studies. Trial 311CUS/0007 evaluated the safety of Zomig Tablets 2.5, 5.0 and 10.0 mg in adolescents (study 1). Trial 311CUS/0005 evaluated the safety and efficacy of Zomig 5mg in adolescent in a two-phase trial. Phase 1 was an acute efficacy trial (study 3) and phase 2 was a long-term safety trial (study 4). In order to meet the requirements of the PK trial (study 2) the sponsor submits 3 PK trials (trials 311CIL/092, 136-007, and D1221C0004). Trial 311CIL/092 evaluated the PK of Zomig 5 mg in healthy adolescents and adults and included non-migrainous subjects. Trial 136-007 evaluated the PK of Zomig 10 mg in adult migraineurs during and between an attack. Trial D1221C0004 evaluated the PK of Zomig Nasal Spray 5 mg in adolescents and adults with a history of migraine.

1.1 Regulatory History and Significant Previous Reviews

- November 25, 1997 — Zomig Tablet (NDA 20-768) approved.
- April 9, 1998 — Sponsor submits results of adolescent PK Study (311CIL/0092) and a new protocol for study 311CUS/0005 (Adolescent efficacy study, Dr. Oliva's review of serial 079 can be found in the Division file).
- September 2, 1998 — Proposed pediatric clinical development plan submitted (Dr. Oliva's review of serial 091 can be found in the Division file).
- March 26, 1999 — Original Pediatric Written Request issued (see Appendix 8.1).
- April 16, 1999 — Sponsor's reply to Written Request submitted (Dr. Oliva's review of serial 100 can be found in the Division file). Also includes results from trial 311CUS/0007 and amendment to study 311CUS/0005.
- May 29, 2002 — Pediatric Written Request Amendment issued (see Appendix 8.2, and below).
- July 3, 2002 — Pediatric Written Request Reissued (see Appendix 8.3, and below).

- August 15, 2002 — Teleconference between the sponsor and Agency (sponsor minutes supplied in serial 153, my personal notes are summarized below and can be found at the end of my review of serial 149 in DFS).
- June 24, 2003 — Sponsor submits new protocol to evaluate the efficacy of Zomig Nasal Spray in adolescents (My review is available in DFS).
- September 3, 2003 — Requested PK data summary submitted in serial N(PU); Biopharmacology Review pending (see comments below).
- September 30, 2003 — Pediatric Exclusivity Determination and labeling changes supplement submitted.

The original Pediatric Written Request letter outlined 4 clinical trials to be completed; an acute adolescent efficacy study, a long term adolescent safety study, an adolescent migraineur PK study, and an adolescent inpatient safety study (if doses greater than 5 mg are proposed). The Pediatric Written Request amendment dated May 29, 2002 changed the timeframe for submitting the completed package to no later than September 30, 2003 otherwise all elements of the original Written Request were unchanged. The Pediatric Written Request reissued on July 3, 2002 did not change the terms of the agreement other than to notify the sponsor that the Written Request has been formally reissued.

The following issues were discussed during the August 15, 2002 teleconference with the sponsor (from my personal notes):

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- *Despite the lack of efficacy seen in Trial 311CUS/0005 we still recommend the long-term safety study outlined in the Written Request. Our reasoning for this request is that (1) a negative trial does not necessarily mean the treatment is ineffective, and (2) there is considerable pediatric use of zolmitriptan.*
- *The sponsor informed us that the long-term study has been terminated but has 313 patients treated for 6 months and 153 patients treated for 1 year. The sponsor was informed that this might meet the requirements of the Written Request however it is necessary that subjects treated approximately 2 migraines per month. The sponsor was requested to determine the number of migraines treated per month on average and let us know.* [Note: We discussed that if the long term study treated slightly less than 2 migraines per month the Written Request will need to be amended. The sponsor did not submit a tally of subjects or the average number of migraines treated per month until 9/30/03.]
- *The already completed PK study was conducted in 21 healthy pediatric and adult patients without a history of migraines. The sponsor states they have a second PK study in adults* (b) (4) *The sponsor was informed that this might be sufficient however it would be a matter of review. Dr. Uppoor requested a summary of each PK study for our review. Additionally it may be argued that it is not ethical to perform a second PK study in pediatric subjects with a migraine history since a PK study in healthy pediatric subjects has already been completed. The sponsor suggested performing a pediatric PK study using zolmitriptan nasal spray however they were informed it would not be helpful in pursuing the Written Request for the tablet formulation.* [Note: The requested summaries were not received until 9/03/03.]

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On September 3, 2003 the sponsor submitted the PK summary requested by Dr. Uppoor during the August 15, 2002 teleconference. A formal review by biopharmacology is pending at this time however contained in the submission is a brief summary of trial 311CIL/0092 (PK trial healthy adolescents vs. healthy adults), trial 136-007 (PK trial in adult migraineurs during and between attacks), and trial D1221C0004 (PK study of Zomig Nasal Spray in adolescents and adults migraineurs between attacks). (b) (4) Each of these trials is further discussed later in this review. Individually neither of these studies addresses the single PK study (study 2) requested in the Pediatric Written Request however the sponsor hopes collectively they will meet the requirements. This issue was discussed at the August 15, 2002 teleconference and the supporting data was requested but not sent in until this September 3, 2003. During the teleconference meeting we agreed we would look at the data and make a decision whether collectively trial 311CIL/0092 and trial 136-007 were sufficient. We clearly informed the sponsor trial D1221C0004 would not be helpful since it involved the use of a nasal spray formulation. We informed them we would consider changing the Written Request if the data was sufficient. Due to the short interim time between receipt of the PK data and receipt of the Pediatric Exclusivity Determination supplement there has been insufficient time to review the data or amend the Written Request (if required).

2. Clinical Review Methods

2.1 How the Review was Conducted

All data submitted by the sponsor for this review is contained in the electronic submission dated September 30, 2003 and can be found at \\CDSESUB1\N20768\S_012\2003-09-30.

2.2 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor asserts that all studies conducted in support of this supplement were conducted according to the procedures and principals of Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki.

2.3 Evaluation of Financial Disclosure

1. For study 311CUS/00005 (Adolescent acute efficacy and long term safety study)

The sponsor has submitted a completed Form FDA 3454 certifying that they have not entered into any prohibited financial agreements with investigators. A single investigator (b) (6) responded positively to receiving sums greater than $25,000 from AstraZeneca. (b) (6) The sponsor does not give any details about the nature or complete amount of moneys provided (b) (6) In the final analysis the study failed so I do not believe this resulted in any significant bias.

2. For study 311CUS/00007 (Adolescent inpatient safety study)
   The sponsor has submitted a completed Form FDA 3454 certifying that they have not entered into any prohibited financial agreements with investigators.

3. Tabular comparison of Pediatric Written Request and Sponsor Reply

The following table summarizes the four studies requested in the Pediatric Written Request (original August 26, 1999). On May 29, 2002 the original pediatric Request was amended in order to provide a later final response date (July 1, 2002 changed to September 30, 2003). No other details have been amended. The format of the table is in compliance with the format recommended by the Pediatric Exclusivity Determination Board. The left column itemizes the details of the Pediatric Written Request for each of the four studies. The right column itemizes the sponsor's reply to each item. Bolded statements reflect where the sponsor deviated significantly from what was requested in the Written Request. Following the table I provide further details of each study as well as my personal commentary.

Table 1 Pediatric Exclusivity Determination Tabular Comparison

Written Request Items*	**Information Submitted/Sponsor's response**
Indication(s) to be studied: The use of zolmitriptan tablets for the acute treatment of migraine headache in adolescents (ages 12 to 17 years).	**Indication(s) studied:** The use of zolmitriptan tablets for the acute treatment of migraine headache in adolescents, ages 12 to 17 years.
Types of studies/ Study Design:	**Types of studies: (Boldfaced text denotes information that differs from the WR.).**
Study 1: Adolescent Inpatient Safety and Tolerability Study if doses greater than (>) 5 mg are proposed for use.	**Study 1 (Trial 311CUS/0007):** The sponsor has conducted the following study: "A Multicenter, Double-Blind, Placebo-Controlled, Randomized, Four Parallel Group Trial for Safety and Tolerability of Zolmitriptan in Adolescent Subjects." This was a safety study involving 84 subjects between the ages of 12 to 17 years (inclusive). Subjects were healthy adolescents with or without a history of migraine. Subjects were equally randomized to Zomig 2.5 mg, Zomig 5 mg, Zomig 10 mg or placebo. Subjects were screened for entry at visit 1. Within 10 days of screening subjects returned to the center for enrollment and randomized treatment. Subjects were followed in-house for at least 4 hours and contacted by telephone at hour 24. Thereafter they were seen for a follow up safety visit within a few days after treatment. Although inpatient monitoring was limited to 4 hours the overall design of the study is acceptable for an adolescent safety and tolerability study.
Study 2: Pharmacokinetic Study.	**Study 2a Trial 311CIL/0092:** "A single dose trial to compare the pharmacokinetics and tolerability of oral 311C90 5 mg in adolescents and adults". This was a single center, open-label, single dose, parallel design study in which the pharmacokinetics of Zomig tablet 5 mg was compared between healthy adolescents and adults. **Study 2b Trial 136-007:** "An Open Study to investigate the Pharmacokinetics and Tolerability of Oral 311C90 and to Obtain a Preliminary Indication of Efficacy in Patients with Migraine". This was a single center, open-label, 2 period study (active migraine, no migraine) in adult migraineurs (18 to 55 years). Subjects were treated with Zomig Tablets 10 mg. PK samples were taken serially for 4 hours. **Study 2c Trial D1221C0004:** "Open Label Nonrandomized Comparison of the Pharmacokinetics of a single 5-mg Dose of Zolmitriptan in Adults and Adolescent Migraineurs when given as Nasal Spray between Migraine Attacks". **Comments:** The sponsor submits 3 PK studies in support of this Exclusivity Request however only the first trial involved adolescents receiving Zomig Tablets. A biopharmacology consult has been requested to assess the adequacy of the sponsor's response.

Study 3: Adolescent Efficacy Study	**Study 3 (Trial 311CUS/0005-Phase 1):** "A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study and Open-label, Long-Term, Tolerability Study with Zolmitriptan (Zomig™) for the Acute Treatment of Migraine Headaches in Adolescent Patients". This was a 2-phase, multicenter, international, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in adolescent patients. In Phase I of the study, patients were randomized to treat a single migraine headache of moderate to severe intensity with 2.5 mg, 5 mg, or 10 mg zolmitriptan, or placebo. Visit 1 of phase 1 included the usual review of entry criteria, complete physical examination, 12-lead ECG, clinical chemistry, hematology, and pregnancy test. Eligible subjects returned to the clinical site (visit 2) for randomization, instructions, and dispensing of study materials. Thereafter subjects were instructed to treat their next migraine of moderate to severe intensity with randomized medication. A final follow up visit (visit 3, within 7 days of treatment) included a physical examination, 12-lead ECG, clinical chemistry, hematology and a pregnancy test. Phase 2 is described under study 4 since the sponsor intends phase 2 to meet the requirements of "study 4" of the Written Request. The overall design of this phase of the study is acceptable for an adolescent efficacy study.
Study 4: Adolescent Long-term Safety Study.	**Study 4 (Trial 311CUS/0005-Phase 2):** "A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study and Open-label, Long-Term, Tolerability Study with Zolmitriptan (Zomig™) for the Acute Treatment of Migraine Headaches in Adolescent Patients". This was a 2-phase, multicenter, international, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in adolescent patients. Phase 1 is described under study 3. Phase 2 was an open label, long term (up to 1 year) safety study in which adolescent subjects treated multiple migraine attacks with Zomig 5 mg. A second dose of Zomig 5 mg was permitted after 2 hours if required for an incomplete response or recurrence. Subjects completing phase 1 of the trial were eligible for entry into phase 2. Safety evaluations during phase 2 included frequent safety visits and follow up telephone contact as well as clinical chemistries, hematology and 12 lead ECGs on visit 5 and 8 (end of study). The overall design of this phase of the study is acceptable for a long-term safety study in adolescents.
Optional Studies:	No optional studies have been conducted and submitted in support of this supplement.
Objectives/rationale	**Objectives/rationale**
Study 1: To evaluate the safety and tolerability of doses >5 mg single doses of zolmitriptan in adolescents 12 to 17 years of age in an inpatient setting.	**Study 1 (Trial 311CUS/0007):** The primary objective of this trial was to evaluate the safety and tolerability of Zomig 2.5, 5 and 10 mg in adolescent patients with or without a history of migraine. Efficacy was not assessed. Subjects were followed inpatient for the first 4 hours after randomized treatment then released to home care with a adverse event diary. A telephone contact was completed at hour 24 and a safety follow visit occurred within 7 days of treatment. The stated objective is acceptable.
Study 2: To evaluate the pharmacokinetics of zolmitriptan in adolescents 12 to 17 years of age with migraine headaches. [Although not stated in the WR, the assumption is zolmitriptan would be in tablet form.]	**Study 2a Trial 311CIL/0092:** The primary objective of this trial was to compare the PK parameters of Zomig tablet 5 mg between healthy adults and healthy adolescents. Twenty-one adolescents between the ages of 12 to 17 were enrolled. **However participants did not necessarily need to have a history of migraine and if they did they were not to have had an attack within 48 hours of testing.** **Study 2b Trial 136-007:** The primary objective of this study was to compare the PK and tolerability of Zomig tablet 10 mg during and between migraine attacks **in adults. No adolescents were included.** Additionally early efficacy data was collected. **Study 2c Trial D1221C0004:** The primary objective of this study was to compare the PK of **Zomig Nasal Spray 5 mg** in adolescents and adults with a history of migraine. Subjects were not expected to have an active migraine.

	Comments: The sponsor has not conducted a PK trial in adolescent migraineurs using Zomig Tablet. The division is on record as having told the sponsor that the 3rd trial would not be useful in meeting the Written Request for the PK study.
Study 3: To evaluate the efficacy and safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.	**Study 3 (Trial 311CUS/0005-Phase 1):** The primary objective of the first phase of the study was to evaluate the efficacy of Zomig Tablet (2.5, 5, and 10 mg) in the treatment of an acute migraine of moderate to severe intensity in adolescent patients (12 to 17 years of age inclusive). The stated objective is acceptable.
Study 4: To evaluate the long-term safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.	**Study 4 (Trial 311CUS/0005-Phase 2):** The objective of the second phase of the study is to evaluate the safety Zomig 5 mg in the treatment of multiple migraine events in adolescents (12 to 17 years of age inclusive) over a period of 1 year. The stated objective is acceptable.
Study Design	**Study Design**
Study 1: Randomized, double-blind, placebo-controlled, parallel group inpatient study in adolescents.	**Study 1 (Trial 311CUS/0007):** This was a randomized, double blind, placebo controlled, **multicenter**, parallel group inpatient study in adolescents. Subjects were screened for entry at visit 1. Eligible subjects returned to the inpatient site within 10 days of screening for randomized treatment (Zomig 2.5 mg, 5 mg, 10 mg or placebo). Once treatment was administered subjects were followed inpatient for at least 4 hours. After 4 hours subjects were released to home in the care of their guardian. Adverse events were monitored for 24 hours. Safety evaluations are described below. A final follow up safety visit occurred within 7 days of treatment. The overall design of the study is an acceptable for a pilot safety and efficacy study.
Study 2: Open label, single dose, parallel group inpatient pharmacokinetic study in adolescents and adults with history of migraine. Ideally, this study should be conducted during a migraine.	**Study 2a Trial 311CIL/0092:** This was an open-label, single dose, parallel group, in-patient pharmacokinetic study in adolescents and adults. **A history of migraine was not required.** Screened subjects were admitted to the clinical site on Day 1, treated with study medication on Day 2, and released to home on Day 3. **Study 2b Trial 136-007:** This was an open label, single center, single dose, inpatient, 2 period/crossover study (active migraine, no migraine) in which 20 adult migraineurs (18 to 55 years) received Zomig 10 mg. PK samples were taken for 4 hours. There was a washout period of at least 48 hours between treatments. **No adolescent subjects were included.** **Study 2c Trial D1221C0004:** This was a two center, open label, single dose, parallel group PK trial in adolescents (12 to 17 years) and adults (18 to 65 years) using **Zomig Nasal Spray 5 mg.** Plasma levels of zolmitriptan and 183C91 were collected for 10 hours. Subjects were not expected to have an active migraine at the time of treatment. **Comments: The sponsor has not conducted the trial requested**. A determination, by the biopharmacology reviewer, of whether the combined 3 studies meet the essential elements of the Written Request is pending at this time.
Study 3: Randomized, double-blind, placebo-controlled, parallel group outpatient study in adolescents.	**Study 3 (Trial 311CUS/0005-Phase 1):** Phase 1 of this study was a randomized, double-blind, placebo-controlled, parallel group study in adolescents. Subjects were screened for entry at visit 1 and instructed on study procedures at visit 2. Thereafter subjects were to treat their next migraine attack of moderate to severe intensity with randomized treatment (Zomig tablet 5 mg or placebo). Within 7 days of treatment subjects were to return to the clinic for a safety evaluation. Safety evaluations are described below. The overall design of this phase of the study is acceptable.
Study 4: Open label, 12-month outpatient study in adolescents.	**Study 4 (Trial 311CUS/0005-Phase 2):** Phase 2 of this study was an open label, long-term (up to 1 year) study in which adolescent subjects (completers from phase 1) treated multiple migraine attacks with study medication. Frequent in office follow up and repeated phone contact occurred during the study. Additionally safety chemistries, hematology and ECGs were done at visit 5 and at the end of the study (exit visit). The design of this phase of the study is acceptable.

Age groups to be studied:	Age group and population in which study was performed:
Study 1: Adolescent patients ages 12 to 17 years, inclusive.	**Study 1 (Trial 311CUS/0007):** Adolescents between the ages of 12 to 17 years (inclusive) were evaluated. The mean age was 14.8 years, 22.6% of subjects were between the age of 12 to 13 years, 35.7% were between the ages 14 to 15 years, and 41.7% were between the ages of 16 to 17 years. The age range of the patient population is acceptable.
Study 2: Adolescent patients ages 12 to 17 years, inclusive	**Study 2a Trial 311CIL/0092:** Twenty-one adolescents between 12 to 17 years of age (inclusive) and 18 adults were included. **Study 2b Trial 136-007: Twenty adult migraineurs (18 to 55 years**) were included (16 females/4 males). **No adolescents were included.** **Study 2c Trial D1221C0004:** Fifteen adolescents (7 females and 8 males) and 15 adults (8 females and 7 males) participated in this study. The mean age of adolescent cohort was 14.4 with a range of 12 to 17. The mean age of the adults was 39.1 years (range 19 to 63 years). **Comments:** Study 2a and 2c included the appropriate age group.
Study 3: Adolescent patients ages 12 to 17 years, inclusive.	**Study 3 (Trial 311CUS/0005-Phase 1):** Adolescents between the ages of 12 to 17 years (inclusive) were evaluated. The mean age of all subjects treated was 14.2 years with 54.3% were between 12 to 14 years of age and 45.7% were between 15 to 17 years of age. As is typical for migraine studies the majority of patients were female (58.6%) and Caucasian (78.7%). Baseline demographics were comparable between cohorts. The age range of the patient population is acceptable.
Study 4: Adolescent patients ages 12 to 17 years, inclusive.	**Study 4 (Trial 311CUS/0005-Phase 2):** Adolescents between the ages of 12 to 17 years (inclusive) were evaluated. The demographics of subjects participating in phase 2 of this study were nearly identical to those of phase 1. The age range of the patient population is acceptable.
Number of patients to be studied or power of study to be achieved:	**Number of patients studied, demographics or power achieved:**
Study 1: A sufficient number of adolescent subjects to be able to assess the acute safety of zolmitriptan at doses > 5 mg.	**Study 1 (Trial 311CUS/0007):** A total of 84 subjects were treated with randomized treatment (21 per cohort). The sponsor did no formal sample size calculations. The sponsor asserts the sample size of 84 subjects was chosen based on practical considerations. The majority of subjects were male (64%) and Caucasian (66%). Treatment cohorts were well balanced for baseline demographics. This reviewer considers the size of the study acceptable for a pilot study.
Study 2: A sufficient number of patients to adequately characterize the single dose pharmacokinetics of adolescents compared to adults.	**Study 2a Trial 311CIL/0092:** In total there were 21 adolescents and 18 adults. The sponsor calculates cohorts of 18 subjects each will provide 88% chance of observing either a 67% increase of a 40% decrease in AUC for adolescents compared to adults. This size is typical for PK studies I have reviewed. **Study 2b Trial 136-007: The sponsor states the choice of 20 subjects was arbitrary.** **Study 2c Trial D1221C0004:** The sponsor states a sample size of 12 subjects per group were required to provide a 90% confidence intervals (CI) of the geometric mean ratio of adolescent to adult for AUC from 0.8xR to 1.25xR, where R is geometric mean ratio. The sample size is adequately powered.

	Comments: Studies 2a and 2c had sufficient number of participants to adequately characterize the PK of a singe dose zolmitriptan in adolescents compared to adults. Study 2a evaluated Zomig Tablet 5 mg. Study 2c evaluated Zomig Nasal Spray 5 mg.
Study 3: A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of headache response. The study should attempt to define the dose-response relationship in this age group, including the identification of a no-effect dose. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.	**Study 3 (Trial 311CUS/0005-Phase 1):** The sponsor estimated that a sample size of 184 patients per cohort would provide 80% power to detect a 15% difference in headache response at 2 hours assuming a placebo response rate of 50% and 65% for Zomig 2.5 mg. This calculation took into consideration a higher placebo response rate than is normally seen in adult migraine studies. A total of 850 subjects enrolled in phase 1 of the trial and 696 subjects took study medication. Treated subjects were equally randomized to placebo (n=175), Zomig 2.5 mg (n=171), Zomig 5 mg (n=171) or Zomig 10 mg (n=179). The mean age of all subjects treated was 14.2 years and were fairly evenly distributed between age groups (54.3% between 12 to 14 years of age and 45.7% between 15 to 17 years of age). The primary endpoint for this phase of the study is headache response at 2 hours defined as moderate to severe pain going to mild or no pain at 2 hours without the use of rescue medication. This endpoint is standard for most migraine studies reviewed in HFD-120 and is considered valid. This reviewer considers the expected relative treatment effect of 15% between Zomig 2.5 mg and placebo clinically relevant. Since multiple doses were evaluated a dose response relationship was theoretically possible however the sponsor previously conceded (serial 100, 4/16/99) that it was possible this study would not determine the "no effect" dose and agreed to conduct a further study if necessary. (b) (4)
Study 4: A sufficient number of adolescent migraine patients to be able to characterize the long-term safety of zolmitriptan when used to treat multiple migraine attacks over one year. Each patient should treat, on average, 2 or more headaches per month. At a minimum, 300 to 600 patients, using the highest planned marketed dose, should be exposed for six months, and 100 patients, using the highest planned marketed dose, should be exposed for one year, There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.	**Study 4 (Trial 311CUS/0005-Phase 2):** The sponsor did not perform a formal power calculation for this phase of the study since the primary endpoint was safety. A total of 680 subjects entered phase 2 of the trial, 603 were included in the safety population (took at least 1 dose of study medication) and 151 subjects completed at least 326 days of the study (study stopped early due to lack of efficacy). The mean age at entry for the safety population was 14.2 years and was fairly well distributed (54.9% between 12 to 14 years of age, 45.1% between 15 to 17 years of age). This age range distribution is acceptable. All subjects treated their migraine with Zomig 5 mg (highest planned marketed dose). The sponsor summarizes exposure by stating "319 patients had exposures up to 180 days and treated 1555 attacks, 239 patients had exposures between 181 to 360 days and treated 4690 attacks, and 42 patients had exposure times greater than 1 year (360 days) treated 989 attacks". This computation appears to include the exposure during phase 1 of the study. **A closer look at the exposure data during phase II of the study demonstrates 281 subjects took Zomig 5 mg for at least 6 months and treated 3408 attacks (approximately 2 attacks/month). Likewise 42 patients took Zomig 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 migraines/month).** In total 151 subjects took Zomig tablet 5 mg for at least 326 days treating approximately 2 migraines per month. Although these numbers are not exactly what was requested the amount of exposure is significant.
Entry criteria:	**Entry criteria used:**
Study 1: Adolescent subjects between 12 and 17 years of age with an average of 1 to 6 IHS defined migraines per month.	**Study 1: (Trial 311CUS/0007):** Entry criteria included a requirement for all subjects to be between the ages of 12 to 17 years of age (inclusive) and have no evidence of significant cardiovascular pathology. **The entry criteria permitted subjects without a history of migraine to enroll and as such it did not specifically state the migraine frequency must be between 1 to 6 migraines per month or whether the migraine must meet the International Headache Society (IHS) definition of migraine**. Since this is a safety study only it seems appropriate that subjects other than migraineurs were included since there is no reason to believe that adolescents with and without a migraine history are otherwise different.

Study 2: Healthy adolescent subjects between 12 and 17 years of age, and healthy adult subjects.	**Study 2a Trial 311CIL/0092:** Entry criteria included a requirement for all subjects (adult and adolescent) to be in good health and with no significant findings on screening evaluations (include CPX, ECG, 24 hour holter, HIV, Hepatitis B serology, pregnancy test, and normal weight). No acute illness was allowed within 2 weeks of study and if the subject had a history of migraine they must not have had an attack within 48 hours of treatment. **Study 2b Trial 136-007:** Entry criteria included a requirement to be **between 18 to 55 years of age** and have a history of IHS migraine (1.1 and 1.2). Migraine frequency had to be between 1 to 6 attacks per month for the previous 3 months. Patients with significant cardiovascular risk factors were excluded. The inclusion/exclusion criteria are typical for adult migraine studies I have reviewed. **Study 2c Trial D1221C0004: Other than stating the age requirements for the study the sponsor does not provide a summary of the entry criteria (full study report not submitted).** Presumably by the nature of the study I would expect that healthy migraineurs were enrolled however I can not confirm this with the information provided by the sponsor. **Comments:** Study 2a entry criteria meet the requirements of the Written Request.
Study 3: Adolescent subjects between 12 and 17 years of age with an average of 1 to 6 IHS defined migraines per month.	**Study 3 (Trial 311CUS/0005-Phase 1):** Subjects were eligible to participate in the study if they were between 12 to 17 years of age (inclusive) and **experienced a minimum of 2 migraines per month meeting the IHS definition for migraine with and without an aura and a maximum of 10 migraine or non-migraine headaches per month.** Other significant criteria included a history of untreated migraine duration of at least 4 hours, and the typical exclusions for triptan products (ex., cardiovascular risk factors, abnormal ECG etc.). Although the entry criteria stipulated a minimum of 2 migraines per month and no more than 10 headaches per month (migraine or nonmigraine) the mean number of migraines per month historically experienced by all subjects was 4.3 with a standard deviation of 2.1. Hence the majority of subject entered into the study had between 2 to 6 migraines per month by history. While the sponsor did not meet the requirements stated in the Written Request it could be argued the majority of subjects had between 2 to 6 IHS migraines per month and that some of the participant may have had as many as 10 migraines per month thus making this a "sicker" and potentially more resistant migraine subpopulation. This reviewer believes this deviation from the Written Request is acceptable. Oddly the original protocol submitted in serial 079 (dated 4/9/98) had the inclusion statement requiring between 1 to 6 migraines per month for the preceding 2 months prior to screening however the sponsor changed this criterion in their February 12, 1999 amendment. This change was noted in Dr. Oliva's review of serial 100 (4/19/99) and he commented the migraine frequency criterion was "reasonably close".
Study 4: Adolescent subjects between 12 and 17 years of age with an average of 1 to 6 IHS defined migraines per month.	**Study 4 (Trial 311CUS/0005-Phase 2):** As per study 3.
Clinical endpoints:	**Clinical endpoints used:**
Study 1: Appropriately frequent standard measures of safety, including acute cardiovascular safety.	**Study 1 (Trial 311CUS/0007):** Safety evaluations included a continuous 24 hour holter monitor, serial vital signs assessments (0.5, 1.0, 2.0 and 4.0 hours), and baseline and hour 4 laboratories (Chemistry panel, CBC, and urinalysis). Vital signs included respiratory rate, temperature, and standing/seated blood pressure and pulse. Additional ECGs were done if there were any signs of ischemia during the first 4 hours of monitoring. These safety assessments are appropriate for migraine studies involving triptan products.

Study 2: Pharmacokinetic measures as appropriate.	**Study 2a Trial 311CIL/0092:** Pharmacokinetic endpoints included: AUC, C_{max}, t_{max}, and $t_{1/2}$ for both the parent compound and its active metabolite 183C91. These PK endpoints are acceptable. **Study 2b Trial 136-007:** Pharmacokinetic endpoints included: AUC_{0-4hrs} and C_{max} for both the parent compound and its active metabolite 183C91. The study report does not include t_{max} or $t_{1/2}$. **Study 2c Trial D1221C0004:** Pharmacokinetic endpoints included AUC, Cmax and $t_{1/2}$ for both the parent compound and its active metabolite 183C91. **Comments:** All three trials assessed appropriate PK measures for their respective trial designs.
Study 3: The proportion of patients achieving a headache response at two hours, along with additional standard migraine efficacy measures, and standard measures of safety (clinical-including signs and symptoms, and laboratory).	**Study 3 (Trial 311CUS/0005-Phase 1):** The primary endpoint for phase 1 of this study was the proportion of patients reporting headache relief at 2 hours defined as moderate to severe headache at baseline going to mild or no pain at 2 hours without the use of rescue medication. Additionally this phase included the usual secondary endpoints such as the proportion of patients reporting an associated symptom (nausea, photophobia, phonophobia) at various times, pain freedom at various times, headache recurrence over 24 hours and the use of rescue medication between 2 to 24 hours. Safety evaluations included appropriate baseline and follow-up assessments such as a physical examination, comprehensive metabolic panel, CBC, urinalysis, 12 lead ECG and pregnancy test. The primary endpoint, secondary endpoint and safety evaluations are acceptable.
Study 4: Appropriately frequent standard measures of safety (clinical-including signs and symptoms, and laboratory).	**Study 4 (Trial 311CUS/0005-Phase 2):** The primary endpoint for phase 2 was the incidence of adverse events over a 1-year period with multiple migraines being treated with Zomig 5 mg. Additional safety assessments included repeat clinical chemistries, CBC, urinalysis, 12-lead ECG and physical examinations at visit 5 and visit 8. Safety visits and a telephone contact occurred on alternating months. Additionally the tolerability of a second dose of Zomig 5 mg (if required) after hour 2 was assessed. This sequence of safety evaluations was previously reviewed by the division and determined to be acceptable. These are standard measures of safety required by this division for long term migraine studies.
Study evaluations	**Study evaluations**
Study 1: Inpatient safety data though 24 hours.	**Study 1 (Trial 311CUS/0007):** Subjects were followed **inpatient for the first 4 hours** after randomized treatment and released to home with an adverse event diary if they were well. A brief telephone evaluation was performed at 24 hours and a final safety evaluation visit was conducted within 7 days of treatment. Inpatient safety surveillance included continuous 24 hour cardiac holter monitoring for ischemic changes (initiated 30 minutes prior to dosing), frequent vital signs assessment (0.5, 1.0, 2.0, and 4.0 hours), and pre-treatment and hour 4 clinical laboratories, CBC and urinalysis. Adverse events were assessed continuously. In this reviewer's opinion the safety data collected is adequate.
Study 2: Reports of relevant pharmacokinetic parameters for the doses described in labeling.	**Study 2a Trial 311CIL/0092:** Pharmacokinetic endpoints included: AUC, C_{max}, t_{max}, and $t_{1/2}$ for both the parent compound and its active metabolite 183C91. These PK endpoints are acceptable. The dose used was 5 mg. **Study 2b Trial 136-007:** Pharmacokinetic endpoints included: AUC_{0-4hrs} and C_{max} for both the parent compound and its active metabolite 183C91. The study report does not include tmax or $t_{1/2}$. **The dose used was 10 mg.** **Study 2c Trial D1221C0004: This trial evaluated the PK of Zomig Nasal Spray 5 mg** (b) (4) **Comments:** Trial 2a provided adolescent PK data that could possibly be used in the label for Zomig Tablet although the data was collected in non-migraineurs (b) (4)

Study 3: Safety and effectiveness data through 24 hours.	**Study 3 (Trial 311CUS/0005-Phase 1):** Screened subjects treated their migraine attack with randomized treatment in the outpatient setting and were followed using a standard 24-hour migraine diary to assess safety and effectiveness. The intensity, duration, and outcome of all adverse events were recorded. Safety evaluations included the standard screening assessments previously described and close follow up within 1 week of treatment. In my opinion safety and efficacy were adequately assessed for the 24-hour period.
Study 4: Safety data as discussed above through one year.	**Study 4 (Trial 311CUS/0005-Phase 2):** Subjects treated multiple migraine attacks over a period of 1 year and were followed using standard 24 hour migraine diaries. The intensity, duration, action taken and outcome of all adverse events were recorded. Subjects were seen at the clinic and called on alternating months during the entire study period. Clinical chemistries, hematology, urinalysis and ECGs were collected on visit 5 and 8. **The study plan included following all patients for one year** (b) (4) Despite the early termination of the study a total 151 subjects completed at least 326 days of treatment. All subjects received a final safety visit at the end of the study. The amount of exposure and safety data collected at 11 and 12 months appears sufficient to this reviewer.
Timing of assessments: if appropriate	**Timing of assessments:**
Study 1: Not specified.	**Study 1 (Trial 311CUS/0007):** Adverse events collected through 24 hours. Baseline laboratory results compared to 4-hour post treatment laboratories, continuous 24 hour Halter monitoring started 30 minutes prior to dosing, Serial vital signs reviewed.
Study 2: Not specified.	**Study 2a Trial 311CIL/0092:** PK sampling was done at 0.5, 1, 1.5, 2, 2,5, 3, 4, 5, 6, 8, 10, 12, and 15 hours after dosing with Zomig tablet 5 mg. **Study 2b Trial 136-007:** PK sampling was done at 0, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after dosing with Zomig tablet 10 mg. **Study 2c Trial D1221C0004: Serial PK samples were collected through hour 10. The brief study synopsis does not provide any further details.** **Comments:** Trial 2a and 2b had adequately timed PK sampling for zolmitriptan and its metabolite.
Study 3: Not specified.	**Study 3 (Trial 311CUS/0005-Phase 1):** Adverse events were collected for the standard 24 hours after treatment. Standard efficacy assessments were done at 30 minutes, 1 hour, and 2 hours and use of rescue medication and headache recurrence was followed out to hour 24. The safety and efficacy assessments are acceptable.
Study 4: Not specified.	**Study 4 (Trial 311CUS/0005-Phase 2):** Phase 2 of this trial did not have any pre-stated efficacy endpoints however subjects were given migraine diaries similar to those used in phase 1 in order to capture standard efficacy data. All efficacy analyses were considered exploratory. Safety was assessed for each 24-hour period in which Zomig medication was used. As with phase 1 the intensity, duration and action taken was assessed for each adverse event. Additionally during phase 2 subjects were seen at the clinic and called at home on alternating months during the study. Complete safety evaluations including laboratories, ECGs and physical were done at visit 5 and visit 8. The timing for safety assessment is acceptable.

Drug specific safety concerns:	Drug specific safety concerns evaluated:
Study 1: As previously discussed in prior communications, we have safety concerns regarding the use of higher than currently approved adult doses in this younger population. For this reason, study 1 (an inpatient safety and tolerability study) is requested.	**Study 1 (Trial 311CUS/0007):** Screening safety assessments included a complete history and physical examination, 12-lead ECG, clinical chemistries, CBC, urinalysis and a pregnancy test. Although not specifically requested in the pediatric Written Request the sponsor conducted close cardiac monitoring using serial vital signs and a 24 hour holter monitoring in order to assess whether Zomig at high doses (10 mg, twice recommended initial dose) causes any significant cardiovascular changes. The cardiovascular changes associated with triptan use are the most common major concern with the use of triptans although the group at the highest risk appears to be older subjects with multiple cardiovascular risk factors. Clinical chemistries were also repeated at 4 hours after dosing. The safety plan is acceptable to this reviewer.
Study 2: Not specified.	**Study 2a Trial 311CIL/0092:** Safety evaluations during this trial included a screening physical, HIV test, Hepatitis B test, standard clinical laboratories, a urine drug screen, pregnancy test, vital signs, 12-lead ECG, and 2-lead 24-hour holter monitor. Day 1 (admission) safety included a urine pregnancy test, a brief physical, and vital signs. Day 2 (treatment day) safety included serial vital signs and a 12-lead ECG at hour 4. Day 3 (discharge) safety included standard clinical laboratories, urine pregnancy test, brief physical, vital signs and a 12-lead ECG. The safety protocol is acceptable. **Study 2b Trial 136-007:** Safety evaluations during the screening visit included a CPX, 12-lead ECG, urinalysis, clinical chemistry panel, CBC, and a urine pregnancy test. Safety evaluations during treatment included serial 12 lead ECGs (baseline, 0.5, 1 and 4 hours), serial vital signs (frequently through 4 hours), frequent adverse events query, baseline CBC, and baseline chemistries. The safety protocols are acceptable. **Study 2c Trial D1221C0004: The trial synopsis provided by the sponsor does not outline safety parameters or findings for this study.** **Comments:** Study 2a and 2b had adequate safety protocols during the trials.
Study 3: Not specified.	**Study 3 (Trial 311CUS/0005-Phase 1):** The safety assessments for phase 1 of this study (previously described) are standard safety measures required by this division for acute migraine studies. No specific or additional safety concerns were described in the Written Request.
Study 4: Not specified.	**Study 4 (Trial 311CUS/0005-Phase 2):** The safety assessments for phase 2 of this study (previously described) are standard safety measures required by this division for long-term migraine studies. No specific or additional safety concerns were described in the Written Request.
Drug information: (Note: The WR does not request specific drug information for each study)	**Drug information:**
Dosage form: Oral tablet **Route of administration:** Oral **Regimen:** To be determined by the development program **Formulation:** Solid oral dosage form.	**Dosage form:** All studies, except trial D1221C0004, used the oral tablet formulation of Zomig. **Route of administration:** All studies, except trial D1221C0004, involved the oral route of study drug administration. **Regimen:** The regimen for each study is outlined in the trial design section for each study. **Formulation:** All studies, except trial D1221C0004, used the solid oral dosage from of Zomig.

Statistical information (statistical analyses of the data to be performed)**:**	**Statistical information** (statistical analyses of the data to be performed)**:**
Study 1: Descriptive analysis of the safety data.	**Study 1 (Trial 311CUS/0007):** The primary safety measures were the incidence, nature and severity of treatment emergent adverse events that occur within 24 hours after dosing. Secondary measures included changes in clinical chemistry, hematology, and urinalysis results (screening versus hour 4). Additionally 24-hour Holter monitors were reviewed for evidence of ischemia, and serial vital signs were evaluated for significant changes. Descriptive statistics were used to describe safety findings. No formal between treatment comparisons were planned in the protocol. This analysis plan is consistent with the Written Request.
Study 2: Descriptive analysis of the pharmacokinetic parameters.	**Study 2a Trial 311CIL/0092:** PK parameters for zolmitriptan and 183C91 were log-transformed and analyzed by ANOVA, using age group as the only factor, to calculate 90% CI of the geometric mean ratio of adolescents and adults for each parameter. Mean, standard error, median and range were determined for all parameters and summarized for the following subgroups: adolescents, female/male adolescents, adults, female/male adults. For each group, least-squares means using an ANOVA model on the log-transformed data were calculated, using age group as the only factor. A 90% confidence interval was then calculated on the basis of the ratio of least-squares means. **Study 2b Trial 136-007:** Descriptive statistics were used to describe pharmacokinetic parameters. Non-parametric tests were used to compare treatment periods. Individual differences between treatment period were estimated and the median difference along with the 95% CI was calculated using a method based on Wilcoxon Signed Rank test. Individual plasma concentration-time plots were produced for each patient for both periods and median plasma concentration-time plots, with ranges, were produced for each analyte**.** **Study 2c Trial D1221C0004:** Pharmacokinetic parameter (AUC and Cmax) were log-transformed and analyzed by ANOVA using age group and gender as factors to calculate 90% CI of the geometric mean ratio of adolescent to adult for each parameter. For each group least-squares mean using ANOVA model on the log-transformed data were calculated. **Comments:** A complete review of the trial results by the biopharmacology reviewer is pending at this time.
Study 3: Assessments of the between group difference on the proportion of patients achieving a headache response at 2 hours by a statistical methodology appropriate to the data generated.	**Study 3 (Trial 311CUS/0005-Phase 1):** The proportion of subjects reporting headache response at 2 hours (primary endpoint of phase 1) in each active cohort was compared to placebo using a logistic regression model using terms for treatment, region, and baseline severity. A step-down approach to control for type 1 error was done starting with Zomig 10 mg. The primary analysis population was the ITT population. All tests used a 2-sided hypothesis test with a significance level of 0.050. This analysis plan was previously reviewed by the Agency statistician and is acceptable.
Study 4: Descriptive analysis of the safety data.	**Study 4 (Trial 311CUS/0005-Phase 2):** Descriptive statistics were used to describe the safety data findings in phase 2 of the trial. This analysis plan is consistent with the Written Request.

Did the sponsor submit proposed labeling?	**Yes.**
Labeling that may result from the studies:	**Labeling proposed by sponsor: (A complete labeling review will be done in a separate review.)**
	(b) (4)
Clinical Pharmacology: Pharmacokinetics: *Special* Populations: Pharmacokinetic results from a pharmacokinetic study in adolescents non-migraineurs will be described. **Clinical Pharmacology: Clinical Studies:** Efficacy results from a double blind, dose ranging study in adolescent migraineurs will be described. **Precautions: Pediatric Use:** The safety and effectiveness in pediatric patients (b) (4) have not been established. **Adverse Reactions:** (b) (4) **Dosage and Administration:** (b) (4) **Patient Information:** How to Use Zomig: Pending Results. **Other;** (not described in Written Request)	**Clinical Pharmacology: Pharmacokinetics: *Special* Populations:** The sponsor does not propose any changes to the "Special Populations" subsection of the Clinical Pharmacology section. (b) (4) . Actually it seems odd to this reviewer that we would suggest including PK data from adolescent non-migraineurs when we requested a PK study in adolescent migraineurs. **Clinical Pharmacology: Clinical Studies:** The sponsor does not propose any changes to this section of labeling. The sponsor intends to describe the failed clinical efficacy study in adolescents in the "Pediatric Use" section of labeling (language described below). **Precautions: Pediatric Use:** The sponsor proposes the following changes: "~~Safety and e~~ Effectiveness of ZOMIG Tablets in pediatric patients has~~ve~~ not been established therefore, ZOMIG is not recommended for use in patients under 18 years of age." The acceptability of this statement will be discussed in my labeling review however I recommend the sponsor include the statement "The safety and effectiveness in pediatric patients (b) (4) have not been established." **Adverse Reactions:** The sponsor does not propose any changes to this section. (b) (4) **Dosage and Administration:** (b) (4) the sponsor does not propose any changes to this section. **Patient Information:** The sponsor does not propose any changes to the patient information label. **Pediatric Use: The sponsor inserts the following description of trial 0005:** (b) (4) I will discuss the adequacy of this statement in my labelling review of this submission however my first impression is that the statement is acceptable.

Format of reports to be submitted:	**Format of reports submitted:** electronic
Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.	The following complete and final study reports were submitted: • Trial 311CUS/0005 (Adolescent efficacy study, acute with long term extension); Final report dated 11 September 2003. Datasets were provided. • Trial 136-007 (PK study in adults during and between migraine attack); Final report dated 8 July 1995. **The datasets for this trial were not submitted with this submission**. • Trial 311CIL/0092 (PK trial in healthy adults and adolescent): Final report dated 6 October 1997. **The datasets for this trial were not submitted.** • Trial 311CUS/0007 (Pilot study to assess efficacy of Zomig Tablets up to 10 mg in adolescents); Final report dated 16 July 1999. **No datasets were submitted**. **The following reports were submitted as abbreviated reports or synopsis reports**: • Trial D1221C0004 (PK study using Zomig Nasal Spray in adolescent and adult migraineurs between attacks**.) A brief synopsis of this study was provided.** The level of details is minimal and no assessment of safety can be adequately determined by what has been submitted. **No datasets were submitted**.
Timeframe for submitting reports of the studies:	**Date study reports were submitted:**
• Reports of the above studies must be submitted to the Agency on or before July 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection of exclusivity that has not expired a [at] the time you submit your reports of the studies in response to this Written Request. (From Original Written Request) • Reports of the studies that meet the terms of the Written Request dated March 26, 1999, as amended by this letter, must be submitted to the Agency on or before September 30, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. (From Amended Written Request May 29, 2002) **Comment:**	The original Written request stated all studies needed to be completed and submitted to the Agency by July 1, 2002. The Pediatric Written Request amendment issued May 29, 2002 changed the date for final submission of the complete response to September 30, 2003. This is the only item amended. The sponsor's response was received on September 30, 2003. **Comment:** The Pediatric Exclusivity Request submission was submitted by the final termination date.
Additional Information:	See section 7 for this review for a discussion of the review team's conclusions and recommendations.

*All Written Request Items are exactly as written in the original Written Request Letter (see Attachment 1) and amended on May 29, 2002 (amended final date for submission only).

What follows is a brief review of each trial submitted in support of this Pediatric Exclusivity Request.

4. Brief Review of Trial 311 CUS/0007 (Study 1)

"A Multicenter, Double-blind, Placebo-controlled, Randomized Four Parallel Group Trial for Safety and Tolerability of Zolmitriptan (ZOMIG) in Adolescent Subjects"

4.1 Design and Schedule of Events

This was a double-blind, randomized, placebo-controlled, 4 parallel group trial in healthy adolescent subjects, with or without history of migraines. Subjects were screened at visit 1 to determine eligibility. Visit 1 assessments included a complete physical examination, vital signs assessment, ECG, a comprehensive metabolic panel, CBC, urinalysis and a urine pregnancy test (if appropriate). Additionally entry criteria and the informed consent were reviewed. Eligible subjects were invited to return to the center for randomized treatment (visit 2) within 7 days of screening. During visit 2 subjects received randomized treatment and followed inpatient for at least 4 hours. Safety evaluations included a continuous 24 hour holter monitor (started 30 minutes prior to dosing), serial vital signs assessments (0.5, 1.0, 2.0 and 4.0 hours), and hour 4 laboratories (Chemistry panel, CBC, and urinalysis). Vital signs included respiratory rate, temperature, and standing/seated blood pressure and pulse. Additional ECGs were done if there were any signs of ischemia during the first 4 hours of monitoring. If subjects reported feeling well they were released to their guardians with a 24-hour adverse event diary (event, duration, intensity, action taken, and outcome collected). All subjects were contacted by telephone at hour 24 to determine status. A final safety visit (visit 3) occurred within 10 days of randomized treatment and included a physical examination and a review of adverse events.

4.2 Patient population

Key entry criteria included all adolescents between the age of 12 to 17 years (inclusive) without any significant medical history. Specifically excluded were adolescents with abnormal screening assessments or history or findings of ischemic heart disease, any vascular disorders, cardiac accessory conduction pathway arrhythmias (e.g.. WPW), hypertension, orthostatic hypotension, epilepsy or convulsive disorder, basilar, hemiplegic or ophthalmoplegic migraine, renal or hepatic impairment, pregnancy or lactation. Subjects were not specifically required to have a history of migraine however if they did the entry criteria specifically excluded subjects who should not receive triptans (ex cardiovascular conditions or unusual migraines such as basilar migraines). Prophylactic migraine medication was prohibited. Concomitant use of SSRIs or cimetidine was prohibited within 24 hours of treatment.

4.3 Results

A total of 84 healthy adolescent subjects (with or without a migraine history) were equally randomized to Zomig 2.5, 5.0 10 mg or placebo in 6 centers. The mean age was 14.8 years (range 12 to 17 years), 22.6% of subjects were between the age of 12 to 13 years, 35.7% were between the ages 14 to 15 years, and 41.7% were between the ages of 16 to 17 years. The majority of subjects were male (64%) and Caucasian (66%). All subjects completed the trial. There were no significant differences between cohorts for baseline demographics.

The following table briefly summarizes the incidence and nature of adverse events experienced in each cohort. Overall there was some evidence of a dose effect in the incidence of subjects reporting at least 1 adverse event as evidenced by the fact that 38.1% of subject randomized to Zomig 2.5 mg

reported at least 1 adverse events compared to 71.4% of subjects randomized to Zomig 5.0 mg. However this trend was not evidenced in the comparison between Zomig 5.0 mg compared to Zomig 10 mg (71.4% vs. 66.7% respectively). There were no serious adverse events, withdrawals due to adverse events, or deaths during the trial. As demonstrated in the following table the most common adverse events were headache, nausea, tightness, somnolence, and dizziness. Nearly all adverse events were rated a mild or moderate in severity. Only 5 (5%) adverse events were rated as severe; thirst (placebo), tightness (2.5 mg), somnolence (2.5 mg), and headache (2.5 and 10 mg).

Table 2 Adverse Events seen during Trial 311 CUS/0007

	Placebo (n=21)	**Zomig 2.5 mg (N=21)**	**Zomig 5.0 mg (n=21)**	**Zomig 10.0 mg (n=21)**
Incidence of subjects reporting $\geq$ 1 AE	28.6%	38.1%	71.4 %	66.7 %
Serious Adverse Events	0	0	0	0
Withdrawals	0	0	0	0
Deaths	0	0	0	0
AEs reported by more than 1 subject in any treatment group				
Abdominal Pain	0	0	0	2 (9.5%)
Asthenia	0	1 (4.8%)	2 (9.5%)	0
Chest Pain	1 (4.8%)	0	0	2 (9.5%)
Headache	2 (9.5%)	6 (28.6%)	4 (19.0%)	5 (23.8%)
Tightness	0	1 (4.8%)	5 (23.8%)	1 (4.8%)
Nausea	2 (9.5%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dizziness	0	0	3 (14.3%)	3 (14.3%)
Hypertonia	0	0	1 (4.8%)	2 (9.5%)
Somnolence	1 (4.8%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dyspnea	1 (4.8%)	0	0	2 (9.5%)

Source: Sponsor table 3 and 4 Trial 311 CUS/0007 study report.

All ECGs were considered normal. There were no clinically relevant changes in vital signs. Thirteen subjects had ST segment depression recorded during Holter monitoring. The sponsor states evaluation of the Holter monitoring results by 2 independent cardiologists indicated that the findings were compatible with tachycardia in 11 of the 13 subjects. In the remaining 2 subjects, the findings were considered to be of undetermined significance by 1 cardiologist; the 2nd cardiologist considered the findings to be of undetermined significance, not ischemic in nature, and probably related to early repolarization. None of the 13 subjects had symptoms suggestive of an ischemic heart event. There were no clinically relevant changes in the metabolic chemistry panel, CBC or urinalysis between screening studies and hour 4. There was no evidence of a relationship between dose and mean changes in urine pH or specific gravity.

4.4 Conclusions/Comments

Overall single oral doses of Zomig 2.5, 5, and 10 mg were well tolerated in adolescent subjects during this study. The nature of adverse events seen during this trial were similar to those seen during adult migraine studies using Zomig tablets except for the higher incidence of headache. Efficacy was not assessed in this study.

5. Brief Review of Contributing Studies to Trial 2 (PK trial)

The sponsor submits the results from 3 PK trials to fulfill the requirements of trial 2 of the written request. The three trials include trial 311CIL/0092 (PK trial healthy adolescents vs. healthy adults), trial 136-007 (PK trial in adult migraineurs during and between attacks), and trial D1221C0004 (PK

study of Zomig Nasal Spray in adolescents and adults migraineurs between attacks). The complete report for trial 311CIL/0092 was submitted to the Agency on April 9, 1998 (serial 079) and is resubmitted with this submission. The final study report for trial 136-007 is submitted with this submission. The final study report for trial D1221C0004 is not provided in this submission however a brief synopsis was submitted earlier on September 3, 2003. The biopharmacology reviewer is assessing the adequacy of this response at this time.

(b) (4)

5.1 Trial 311CIL/0092 (PK trial healthy adolescents vs. healthy adults)

Title: "A Single Dose Trial to Compare the Pharmacokinetics and Tolerability of Oral 311C90 5 mg in Adolescents and Adults"

Purpose: To assess the PK and tolerability of a single dose of Zomig 5 mg tablet in healthy adolescents (12-17 years) compared to adults (18 to 65 years).

Method: Single center, open label, parallel group trial. Serial plasma samples were collected for 15 hours. Note these are non-migraineurs.

Statistical Issues: PK parameters (AUC and Cmax) were log-transformed and analyzed using ANOVA, using age group as the only factor. The 90% CI and the least square means were calculated. For t½, untransformed data were analyzed using ANOVA with age as factor, to calculate the 90% CI for the difference between the means of adolescents and adults.

Results: A total of 39 subjects enrolled [21 adolescents (13 females and 8 males) and 18 adults (12 females, and 6 males)]. Mean age was 14.5 years and 39.1 years for each cohort.

The following table demonstrates the PK parameters for zolmitriptan tablet.

(b) (4)

(b) (4)

The following table presents the adolescent PK results for the active metabolite 183C91.

(b) (4)

5.2 Trial 136-007 (PK trial in adult migraineurs during and between attacks)

Title: "An Open Study to investigate the Pharmacokinetics and Tolerability of Oral 311C90 and to Obtain a Preliminary Indication of Efficacy in Patients with Migraine"
Purpose: To compare the PK and tolerability of Zomig tablet 10 mg during and between migraine attacks in adults.
Method: This was a single center open-label, 2 period study (active moderate/severe migraine, no migraine) in adult migraineurs (18 to 55 years). PK samples were taken for 4 hours.
Results: A total of 20 subjects participated (4 male, 16 female) in the study. The mean age was 38.

(b) (4)

5.3 Trial D1221C0004 (PK study of Zomig Nasal Spray in adolescents and adults migraineurs between attacks, Preliminary Results)

Title: "Open Label, Nonrandomized Comparison of the Pharmacokinetics of a single 5-mg Dose of Zolmitriptan in Adults and Adolescent Migraineurs when given as a Nasal Spray between Migraine Attacks"

Purpose: To compare the PK of Zomig Nasal Spray 5 mg in adolescents and adults with a history of migraine.

Method: This was a two center, open label, single dose, parallel group trial in adolescents (12 to 17 years) and adults (18 to 65 years). Plasma levels of zolmitriptan and 183C91 were collected for 10 hours.

Statistical Issues: Pharmacokinetic parameter (AUC and Cmax) were log-transformed and analyzed by ANOVA using age group and gender as factors to calculate 90% CI of the geometric mean ratio of adolescent to adult for each parameter. For each group least-squares mean using ANOVA model on the log-transformed data were calculated.

Results: A total of 30 subjects participated [15 adolescents (7 females, 8 males); 15 adults (8 females, 7 males)] in the study. The mean age (range) was 14.4 (12 to 17) and 39.1 (19 to 63) respectively.

The following tables summarize the PK findings for zolmitriptan in adults and adolescents.

(b) (4)

(b) (4)

5.4 Conclusions/Comments

(b) (4)

(b) (4)

6. Brief review of Trial 311CUS/0005 (Study 3 and 4)

"A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study and Open-label, Long-Term, Tolerability Study with Zolmitriptan (Zomig™) for the Acute Treatment of Migraine Headaches in Adolescent Patients"

6.1 Design and Schedule of Events

This was a 2-phase, multicenter, international, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in the acute treatment of migraine headache in adolescent patients. In phase 1 of the study, patients were randomized to treat a single migraine headache with either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo. In the phase 2, open-label portion of the study, patients treated multiple migraine headaches over a 12-month period with 5.0 mg zolmitriptan (tablet form). A second 5.0 mg tablet was allowed in phase 2, if necessary, between 2 hours and 24 hours after the 1st dose of study treatment. The sponsor intends phase 1 to meet the requirements of "study 3" of the Written Request and phase 2 to meet the requirements of "study 4" of the Written Request.

The primary objective of the first phase of the study is to evaluate the efficacy of Zomig Tablet (2.5, 5, and 10 mg) in the treatment of an acute migraine of moderate to severe intensity in adolescent patients. The objective of the second phase of the study is to evaluate the safety of Zomig 5 mg in the treatment of multiple migraine events over a period of 1 year. In phase 2 of the trial subjects were permitted to treat migraines at any time including when the pain intensity was mild (1). Additionally subjects were permitted to use a second dose of Zomig 5 mg after 2 hours if they had a migraine recurrence or an incomplete response to the first dose.

Visit 1 of phase 1 included the usual review of entry criteria, complete physical examination, 12-lead ECG, clinical chemistry, hematology, and pregnancy test. Eligible subjects returned to the clinical site (visit 2) for randomization, instructions, and dispensing of study materials. Thereafter subjects were instructed to treat their next migraine of moderate to severe intensity with randomized medication. A final follow up visit (visit 3, within 7 days of treatment) included a physical examination, 12-lead ECG, clinical chemistry, hematology and a pregnancy test.

The schedule of events for phase 2 are summarized in the following table.

Table 13 Schedule of events; phase 2

Assessment	Visit 3 Phase II (training)[a]	5-week telephone contact	Visit 4 After HA	5-week telephone contact	Visit 5 After HA	5-week telephone contact	Visit 6 After HA	5-week telephone contact	Visit 7 Post-HA	5-week telephone contact	Visit 8
Physical exam											√[b]
Electrocardiogram					√						√[b]
Clinical chemistry/hematology					√						√[b]
Pregnancy test											
Dosing, diary card instructions	√	√	√	√	√	√	√	√	√	√	
Study drug dispensed	√		√		√		√		√		
Diary card dispensed	√		√		√		√		√		
Diary card returned			√		√		√		√		√[b]
Unused study drug returned			√		√		√		√		√[b]
Review of diary card			√		√		√		√		√[b]
Quality-of-life questionnaire	√		√		√		√		√		√[b]
Review of adverse experiences		√	√	√	√	√	√	√	√	√	√[b]
End-of-study form completed											√[b]

[a] Visit 3 Phase I is the same visit as Visit 3 Phase II.
[b] End of study or when withdrawal from the study occurs
HA Headache
Data source: Study protocol

6.2 Patient Population

Subjects were eligible to participate in the study if they were between 12 to 17 years of age (inclusive) and experienced a minimum of 2 migraines per month meeting the IHS definition for migraine with and without an aura and a maximum of 10 headaches (migraine or non-migraine headaches) per month. Other significant criteria included a history of untreated migraine duration of at least 4 hours, and the typical exclusions for triptan products (ex., cardiovascular risk factors, abnormal ECG etc.). Patients who completed phase 1 of the trial were eligible for entry into phase 2 of the trial.

A total of 850 subjects enrolled in phase 1 of the trial and 696 subjects took study medication. Treated subjects were equally randomized to placebo (n=175), Zomig 2.5 mg (n=171), Zomig 5 mg (n=171) or Zomig 10 mg (n=179). The mean age of all subjects treated was 14.2 years with 54.3% being between 12 to 14 years of age and 45.7% being between 15 to 17 years of age. As is typical for migraine studies the majority of patients were female (58.6%) and Caucasian (78.7%). Baseline demographics were comparable between cohorts. Although the entry criteria stipulated a minimum of 2 migraines per month and no more than 10 headaches per month (migraine or nonmigraine) the mean number of migraines per month historically experienced by subjects was 4.3 with a standard deviation of 2.1. Hence the majority of subject entered into the study had between 2 to 6 migraine per month by history.

A total of 680 subjects entered phase 2 of the trial, 603 were included in the safety population (took at least 1 dose of study medication) and 151 completed the study (defined as >326 days by the sponsor). Overall 452 subjects (75%) discontinued from the study however many of these withdrawals were due to early termination of the study (110 patients). Fifty subjects (8.3%) withdrew due to an adverse event and 54 (9.0%) withdrew due to ineffectiveness of the trial medication. The baseline demographics of subjects entering phase 2 of the study were similar to those of subjects in phase 1.

The sponsor summarizes exposure by stating "*319 patients who had exposures up to 180 days treated a total of 1555 attacks, 239 patients who had exposures between 181 to 360 days treated a total of 4690 attacks up through 360 days, and 42 patients had exposure times greater than 1 year*

(360 days) and treated a total of 989 attacks 1 year (360 days) treated 989 attacks". This computation appears to include the exposure during phase 1 of the study. A closer look at the exposure data during phase II of the study demonstrates 281 subjects took Zomig 5 mg for at least 6 months and treated 3408 attacks (approximately 2 attacks/month). Likewise 42 patients took Zomig 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 migraines/month). However 151 subjects took Zomig tablet 5 mg for at least 326 days and treated approximately 2 migraines per month.

6.3 Efficacy Results

The primary endpoint for phase 1 of the study was a comparison of the proportion of patients reporting headache relief at 2 hours. Headache relief is defined as moderate (2) or severe (3) headache pain at baseline going to mild (1) or none (0) at 2 hours without the use of rescue medication. Significant secondary endpoints included the incidence of migraine associated symptoms (nausea, photophobia, phonophobia at various times), pain freedom at various times, use of escape medication over 24 hours, and headache recurrence over 24 hours. There were no prespecified efficacy variables during phase 2 of the study although some efficacy data was collected (for exploratory analysis). Headache response (primary endpoint of phase 1) was analyzed using a logistic regression model using terms for treatment region, and baseline severity. The primary analysis population was the ITT population. All tests used a 2-sided hypothesis test with a significance level of 0.050.

The following table briefly summarizes the sponsor's analysis of the primary endpoint and selected secondary endpoints. (b) (4)

(b) (4)

6.4 Safety Results

The primary objective of phase 2 of the study was to evaluate safety over a 1-year period. Safety information was presented using descriptive statistics. No formal analysis of safety was performed. There were no deaths or treatment related serious adverse events in either phase of the trial.

6.4.1 Phase 1:

Six patients randomized to Zomig withdrew due to an adverse event [4 in Zomig 10 mg (1.9%), 2 in Zomig 2.5 mg (1.0%)] compared to no patients randomized to placebo in phase 1 of the trial. The cited reasons for discontinuation are listed in the following table.

Table 15 Adverse Events resulting in Discontinuation, Phase 1

Patient ID	Treatment	Event
0017/0152	Zomig 10 mg	Paresthesia, lymphadenopathy, tightness
0026/0438	Zomig 10 mg	Pain, conjunctivitis, heaviness, tightness
0038/2127	Zomig 2.5 mg	Headache
0041/2041	Zomig 10 mg	Vasodilation (flushed head)
0048/1697	Zomig 10 mg	Dyspnea, stiffness, tightness
0251/2463	Zomig 2.5 mg	Abnormal MRI (no details provided)*

*subject did not use study medication.

There was a single serious adverse event in phase 1; a subject randomized to Zomig 5 mg (PID 0038/2014) reported "prolonged migraine headache" after taking Zomig 5 mg. This event ultimately resulted in hospitalization. He was released several days later with a final diagnosis of labyrinthitis and sinusitis.

The following table briefly summarizes the adverse events occurring in at least 5% of patients in any treatment group seen during phase 1 of this trial. In general the occurrence of adverse events were generally higher with active treatment compared to placebo. The most common adverse events in phase 1 across all zolmitriptan groups were tightness (6.7%), dizziness (6.1%), nausea (5.5%), and paresthesia (4.2%) compared with 1.1%, 2.3%, 1.1%, and 0 for these same events, respectively, in the placebo group. Seventy four percent of all adverse events reported by subjects randomized to Zomig (all doses) was rated as mild to moderate compared to 90% for placebo.

Table 16 AEs occurring in ≥ 5% of patients in any cohort, Safety population, Phase 1

COSTART term	Treatment group number (%) of patients					
	Zolmitriptan 10.0 mg N=178	Zolmitriptan 5.0 mg N=174	Zolmitriptan 2.5 mg N=171	All zolmitriptan N=523	Placebo N=176	All treatments N=699
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All patients with adverse events (AEs)	79 (44.4)	45 (25.9)	49 (28.7)	173 (33.1)	22 (12.5)	195 (27.9)
Tightness	20 (11.2)	10 (5.8)	5 (2.9)	35 (6.7)	2 (1.1)	37 (5.3)
Dizziness	16 (9.0)	8 (4.6)	8 (4.7)	32 (6.1)	4 (2.3)	36 (5.2)
Nausea	14 (7.9)	5 (2.9)	10 (5.9)	29 (5.5)	2 (1.1)	31 (4.4)
Paresthesia	11 (6.2)	8 (4.6)	3 (1.8)	22 (4.2)	0	22 (3.2)
Asthenia	9 (5.1)	2 (1.2)	3 (1.8)	14 (2.7)	2 (1.1)	16 (2.3)
Pain	9 (5.1)	3 (1.7)	3 (1.8)	15 (2.9)	0	15 (2.2)

[a] This table includes the number of patients reporting an adverse event at least once; patients reporting nonserious adverse events outside of the 24-hour time window are not included in the table.

[b] The decreasing order of frequency is based on the 10.0 mg zolmitriptan group.

N Number of patients; n number of patients with adverse events.

Data derived from Table T26.3, Section 11.1.

In general women randomized to zolmitriptan (all doses) reported more adverse events then men (20.7% vs. 12.4%). In the placebo group slightly more men reported an adverse event than women (5.7% female vs. 6.8% male). There were no significant differences between genders for the type and nature of adverse event reported. There were too few non-Caucasians in this study to make a meaningful comparison of adverse events by race. The percentage of adverse events reported for all zolmitriptan patients aged 12 to 14 years (18.0%) was slightly higher but generally similar to the percentage of adverse events reported for all zolmitriptan patients aged 15 to 17 years (15.1%).

There were no clinically significant changes in mean safety laboratories, vital signs, or ECG measurements and were similar between cohorts. There was a single pregnancy during phase 1 of this study that went to term without any complications.

6.4.2 Phase 2

A total of 50 (8.3%) subject withdrew from phase 2 of the study due to an adverse event. Common reasons for withdrawing included continued migraine/headache, parasthesias, tightness, nausea, asthenia, pharyngitis and dizziness. The following 10 (1.7%) subjects reported a serious adverse events. According to the sponsor only 2 of these events occurred within 24 hours of treatment however from the narratives I am only able to ascertain that the malaise case occurred within several hours of taking study medication. No serious adverse events were considered by the investigators to be related to study medication. I reviewed each narrative and agree with the investigator's assessment.

Table 17 Serious AE, Phase 2

Patient ID	Event
0001/0301	Intractable migraine
0001/1405	Intractable migraine
0008/0085	Diabetes mellitus
0013/0250	Abdominal pain
0020/0140	Tonsilar Abscess
0041/0762	Ulcerative Colitis
0651/2302	Malaise*
0011/0323	Increased Migraine
0026/0032	Injury with multiple spinal fractures
0036/0702	Migraine

*Occurred within 24 hours of treatment

Despite the early termination of this trial the sponsor reports that 319 subjects had exposures "up to 180 days" treating a total of 1555 attacks and 239 patients had exposures "between 181 to 360 days" treating a total of 4690 attacks. Forty-two subjects had exposure times greater than 1 year treating a total of 989 attacks. The study report does not clearly state how many subjects received at least 6 months of treatment (180 days) and how many received at least 1 year of treatment (360 days) during phase II of the study. This information was requested from the sponsor during this review. In response the sponsor reports that during phase II, 281 subjects took Zomig 5 mg for at least 6 months and treated 3408 attacks (approximately 2 attacks/month) and 42 patients took Zomig 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 migraines/month). However 151 subjects took Zomig tablet 5 mg for at least 326 days and treated approximately 2 migraines per month. Although these numbers are not exactly what was requested in the Written Request the amount of exposure is significant.

The following table summarizes the most common adverse events seen during the long-term phase of trial 005 by duration of study. The most common adverse events reported during phase 2 of the trial were dizziness (14.5%), nausea (14.3%), tightness (12.0%), and paresthesia (9.5%) at the patient level. Overall 351 (58.2%) patients in the safety population (603) reported at least 1 adverse event and 279 (46.3%) patients reported at least 1 adverse event within the 24-hour time window at the patient level. Across 7253 individual attacks, adverse events were associated with 1209 (16.7%) attacks. There appeared to be no association between the adverse events experience and the length of time exposed to study medication. At the attack level, 974 (80.8%) of all adverse events were rated as mild or moderate.

Table 18 Common AEs, Zomig 5 mg Safety Population, Phase 2

	Patient level					
	30 days N=109	**90 days N=44**	**180 days N=30**	**270 days N=24**	**360 N=59**	**Total N=603**
Dizziness	16 (14.7%)	6 (13.6%)	4 (10.8%)	4 (16.7%)	8 (13.6%)	87 (14.5%)
Nausea	15 (13.8%)	7 (15.9%)	3 (8.1%)	7 (29.2%)	11 (18.6%)	86 (14.3%)
Tightness	14 (12.8%)	5 (11.4%)	2 (5.4%)	3 (12.5%)	6 (10.2%)	72 (12.0%)
Paresthesia	13 (11.9%)	8 (18.2%)	2 (5.4%)	3 (12.5%)	8 (13.6%)	57 (9.5%)
Pharyngitis	9 (8.3%)	7 (15.9%)	3 (8.1%)	3 (12.5%)	7 (11.9%)	48 (8.0%)
Pain	9 (8.3%)	1 (2.3%)	0	1 (4.2%)	8 (13.6%)	44 (7.3%)
Asthenia	8 (7.4%)	2 (4.6%)	1 (2.7%)	2 (8.3%)	3 (5.1%)	38 (6.3%)
	Attack Level					
	30 days N=209	**90 days N=242**	**180 days N=280**	**270 days N=420**	**360 N=1598**	**Total N=7253**
Dizziness	13 (6.2)	8 (3.3)	3 (1.1)	10 (2.4)	8 (0.5)	118 (1.6)
Nausea	12 (5.7)	8 (3.3)	6 (2.1)	18 (4.3)	10 (0.6)	147 (2.0)
Tightness	14 (6.7)	7 (2.9)	22 (7.9)	17 (4.1)	61 (3.8)	267 (3.7)
Paresthesia	14 (6.7)	12 (5.0)	11 (3.9)	11 (2.6)	46 (2.9)	204 (2.8)
Pharyngitis	10 (4.8)	7 (2.9)	3 (1.1)	8 (1.9)	4 (0.3)	60 (0.8)
Pain	9 (4.3)	0	9 (3.2)	3 (0.7)	13 (0.8)	84 (1.2)

There were no clinically significant changes in mean safety laboratory values, vital signs, of ECGs measurements. I reviewed the individual changes for each laboratory assessment and no significant trends were apparent. There were 2 pregnancies during phase 2 of the study. Both resulted in healthy newborns.

6.5 Conclusions/Comments

(b) (4)

Zomig tablets up to 10 mg were well tolerated in the acute, single migraine phase of the trial. Zomig 5 mg was well tolerated in the long-term, open label phase 2 of trial 0005. In both phases the most common adverse events seen were typical of triptan products in adults and are consistent with the current label for Zomig.

7. Conclusions and Recommendations

7.1 Conclusions

A description of minor and significant deviations from the Written Request is outlined in the table 1 of this review. In this section I will further clarify my opinion of the more significant deviations. The Pediatric Exclusivity Review Board is scheduled to meet on December 8, 2003.

Overall study 1 (Trial 311CUS/0007, adolescent inpatient safety study using Zomig tablet 2.5, 5, 10 mg or placebo) was adequately designed for an inpatient safety study in adolescents. Although subjects were monitored inpatient for only 4 hours they were actually closely followed with a holter monitor and an event diary for 24 hours and had a final follow up visit. Since the expected half-life of Zomig tablets is 3 hours in adults this period of close observation should be adequate (in adults the Tmax is 1.5 hours and the elimination half-life is 3 hours). I do not believe 24-hour inpatient safety data would have provided any additional information. Since the primary objective of the study was to evaluate safety the sponsor did not include a history of migraine in the entry criteria. Although we requested adolescent migraineurs be included (frequency of 1 to 6 HIS headache per

month) this deviation seems acceptable to this reviewer. The only objection I have to this plan is that it might have been more acceptable ethically to expose adolescent migraineurs to Zomig as compared to healthy adolescents with nothing to gain but financial compensation and/or personal satisfaction. Since efficacy was not assessed I do not believe this deviation was significant. The completed study report for this trial was submitted on September 30, 2003.

Overall Trial 311CUS/005 (study 2 and 3 of Written Request, phase 1 acute efficacy, phase 2 long-term safety) was adequately designed for an outpatient acute efficacy and long term safety study in adolescents. The objectives for both parts were adequate however the entry criteria did not specify that subjects must have between 1 to 6 IHS defined migraines per month. Instead the criteria stipulated subjects must have at least 2 IHS migraines per month and no more than 10 headaches (migraine and non-migraine) per month. I believe this change is insignificant since the majority of participant had between 2 to 6 migraines per month (mean of 4.3, standard deviation of 2.1) and some could have as many as 10 migraines per month possibly making this a more severe subgroup of adolescent migraineurs than originally planned. The only significant deficiency I see from this study is the lack exposure of at least 300 subjects for 6 months and 100 subjects for 1 year treating at least 2 migraines per month (divisional and ICH standard). (b) (4) This deficiency was discussed at the August 15, 2002 teleconference and the sponsor was asked to supply their exposure numbers in case the Written Request need to be amended however the actual 6 month and 1 year exposure numbers were not supplied until I requested them in an e-mail (October 8, 2003). Although this may be a problem to the Pediatric Exclusivity Review board this reviewer believes the exposure numbers are adequate to make a reasonable assessment of the safety of Zomig Tablets in adolescents. (b) (4)

The sponsor did not conduct the single PK study described as study 2 in the Written Request. Instead the sponsor submitted the results of 3 PK trials as outlined in table 1. This approach was discussed with the sponsor during the August 15, 2002 teleconference and we requested a brief summary of each trial in case the Written Request needed to be amended. The brief summaries were not provided until September 3, 2003, too late to enable a proper review and a change in the Written Request (if required). Additionally at the teleconference we informed the sponsor that trial D1221C0004 (Adolescent PK trial using Zomig Nasal Spray) would not be helpful in meeting the terms of the Written Request for Zomig tablets. A biopharmacology consult has been requested to assess the adequacy of the PK studies in meeting the terms and spirit of the Written Request. To date the consult is still pending. Significant deficiencies which must be considered include the following: adolescent migraineurs were not included in any of the PK studies using Zomig Tablets and the complete study report for trial D1221C0004 was not submitted. (b) (4)

(b) (4)

7.2 Medical Officer Recommendations

In the final analysis I believe the sponsor has made a fair attempt to address all the elements itemized in the Written Request and Exclusivity should be granted. (b) (4)

8. Appendix

8.1 Original Pediatric Written Request (March 26, 1999)

DEPARTMENT OF HEALTH & HUMAN SERVICES

INDEX 109

99/107

Food and Drug Administration
Rockville MD 20857

IND (b) (4)
NDA 20-768

COPY 4

MAR 26 1999

ZENECA PHARMACEUTICALS
ATTENTION: KEVIN MCKENNA, PHD
1800 CONCORD PIKE
PO BOX 15457
WILMINGTON, DE 19850-5437

Dear Dr. McKenna:

Reference is made to your Proposed Pediatric Study Request submitted on September 2, 1998 for Zomig (zolmitriptan) Tablets to IND (b) (4)

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

Types of studies:

Study 1: Adolescent Inpatient Safety and Tolerability Study if doses greater than (>) 5 mg are proposed for use.

Study 2: Pharmacokinetic Study

Study 3: Adolescent Efficacy Study

Study 4: Adolescent Long-Term Safety Study

Objectives/rationale:

Study 1: To evaluate the safety and tolerability of doses > 5 mg single doses of zolmitriptan in adolescents 12 to 17 years of age in an inpatient setting.

Study 2: To evaluate the pharmacokinetics of zolmitriptan in adolescents 12 to 17 years of age compared to adults.

Study 3: To evaluate the efficacy and safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.

Study 4: To evaluate the long-term safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.

Indication(s) to be studied:

The use of zolmitriptan tablets for the acute treatment of migraine headache in adolescents, ages 12 to 17 years.

Study design

Study 1: Randomized, double-blind, placebo-controlled, parallel group inpatient study in adolescents.

Study 2: Open label, single dose, parallel group inpatient pharmacokinetic study in adolescents and adults with history of migraine. Ideally, this study should be conducted during a migraine.

Study 3: Randomized, double-blind, placebo-controlled, parallel group outpatient study in adolescents.

Study 4: Open label, 12-month outpatient study in adolescents.

Age groups to be studied

Adolescent patients ages 12 to 17 years, inclusive.

Number of patients to be studied or power of the study to be achieved

Study 1: A sufficient number of adolescent subjects to be able to assess the acute safety of zolmitriptan at doses > 5 mg.

Study 2: A sufficient number of patients to adequately characterize the single dose pharmacokinetics of adolescents compared to adults.

Study 3: A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of headache response. The study should attempt to define the dose-response relationship in this age group, including the identification of a no-effect dose. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Study 4: A sufficient number of adolescent migraine patients to be able to characterize the long-term safety of zolmitriptan when used to treat multiple migraine attacks over one year. Each patient should treat, on average, 2 or more headaches per month. At a minimum, 300 to 600 patients, using the highest planned marketed dose, should be exposed for six months, and 100 patients, using the highest planned marketed dose, should be exposed for one year. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Entry criteria (i.e., inclusion/exclusion criteria)

Study 1: Adolescent subjects between 12 and 17 years of age with an average of 1 to 6 IHS defined migraine headaches per month.

Study 2: Healthy adolescent subjects between 12 and 17 years of age, and healthy adult subjects.

Study 3: Adolescent subjects between 12 and 17 years of age, with an average of 1 to 6 IHS defined migraine headaches per month.

Study 4: Adolescent subjects between 12 and 17 years of age, with an average of 1 to 6 IHS defined migraine headaches per month.

Clinical endpoints

Study 1: Appropriately frequent standard measures of safety, including acute cardiovascular safety.

Study 2: Pharmacokinetic measures as appropriate.

Study 3: The proportion of patients achieving a headache response at two hours, along with additional standard secondary migraine efficacy measures, and standard measures of safety (clinical—including signs and symptoms, and laboratory).

Study 4: Appropriately frequent standard measures of safety (clinical—including signs and symptoms, and laboratory)

Study evaluations:

Study 1: Inpatient safety data through 24 hours.

Study 2: Reports of relevant pharmacokinetic parameters for the doses described in labeling.

Study 3: Safety and effectiveness data through 24 hours.

Study 4: Safety data as discussed above through one year.

Drug information:

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Formulation: solid oral dosage form

Safety concerns: As previously discussed in prior communications, we have safety concerns regarding the use of higher than currently approved adult doses in this younger population. For this reason, study 1 (an inpatient safety and tolerability study) is requested.

Statistical information, including:

Study 1: Descriptive analysis of the safety data.

Study 2: Descriptive analysis of the pharmacokinetic parameters.

Study 3: Assessment of the between group difference on the proportion of patients achieving a headache response at 2 hours by a statistical methodology appropriate to the data generated.

Study 4: Descriptive analysis of the safety data.

Labeling that may result from these studies

INDICATON:

(b) (4)

CLINICAL PHARMACOLOGY: **Pharmacokinetics**: *Special Populations*:

Pharmacokinetic results from a pharmacokinetic study in adolescents non-migraineurs will be described.

CLINICAL PHARMACOLOGY: **Clinical Studies**:

Efficacy results from a double blind, dose ranging study in adolescent migraneurs will be described.

PRECAUTIONS: **Pediatric Use**:

The safety and effectiveness in pediatric patients (b) (4) have not been established.

ADVERSE REACTION: (b) (4)

(b) (4)

DOSAGE AND ADMINISTRATION: (b) (4)

(b) (4)

PATIENT INFORMATION: **How to Use ZOMIG**

Pending Results.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before July 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired a the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*, with FDA before developing pediatric protocols. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

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

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

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

If you have any questions, call Lana Y. Chen, Project Manager, at 301-594-5529.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evalulaion and Research

8.2 Pediatric Written Request Amendment (4/29/02)

IND (b) (4)

2002/200
Zomig
IND (b) (4)

AstraZeneca Pharmaceuticals LP
Attention: Ms. Judy Firor
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Dear Ms. Firor:

Please refer to your correspondence dated November 13, 2001, requesting changes to FDA's March 26, 1999, Written Request for pediatric studies for zolmitriptan.

We reviewed your proposed changes and are amending the timeframe of the Written Request. All other terms stated in our Written Request issued on March 26, 1999 remain the same.

Reports of the studies that meet the terms of the Written Request dated March 26, 1999, as amended by this letter, must be submitted to the Agency on or before September 30, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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

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

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

If you have any questions, call Lana Chen, Regulatory Project Manager, at 301-594-5529.

Sincerely,

{See appended electronic signature page}

Rachel E. Behrman, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

8.3 Pediatric Written Request Reissue (7/3/02)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-768

Zeneca Pharmaceuticals
Attention: Kevin McKenna, Ph.D.
1800 Concord Pike
P.O. Box 15457
Wilmington, DE 19850-5437

Dear Dr. McKenna:

Please refer to the Written Request, originally issued on March 26, 1999, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using zolmitriptan. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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

/s/

Kevin Prohaska
12/2/03 11:47:12 AM
MEDICAL OFFICER

Eric Bastings
12/2/03 02:07:09 PM
MEDICAL OFFICER