

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-450

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-450 SUPPL #

Trade Name Zomig Nasal Spray Generic Name Zolmitriptan

Applicant Name AstraZeneca HFD- 120

Approval Date 9/26/03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / x / NO / _ /
- b) Is it an effectiveness supplement? YES / _ / NO / x /

If yes, what type (SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / x / NO / _ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe

the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES / _ / NO / x /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO / x /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO / x /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / x /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / x / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-768 Zomig tablets

NDA # 21-231 Zomig-ZMT

NDA #

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2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

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NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly

available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / x / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / x /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / x /

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / x /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Trial 022

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / x /

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / x /
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # Trial 022

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

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(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 53,848 YES / x / NO / ___ / Explain:

Investigation #2

IND # _____ YES / ___ / NO / ___ / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ ! NO / ___ / Explain _____ !

_____ !
_____ !

Investigation #2

YES / ___ / Explain _____ ! NO / ___ / Explain _____ !

_____ !
_____ !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all

rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Russell Katz
9/30/03 04:16:45 PM

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 21-450 Zomig Nasal Spray Supplement Type (e.g. SE5):

Supplement Number:

Stamp Date: 3/27/03

Action Date: 9/26/03

HFD -120 Trade and generic names/dosage form: zolmitriptan nasal spray

Applicant: AstraZeneca

Therapeutic Class: 3S

Indication(s) previously approved:

Migraine – Deferred

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Migraine

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Sponsor conducted studies following March 26, 1999 Written Request for Zomig Tablets (NDA 20-768, IND 45,147)

Date studies are due (mm/dd/yy): 9/30/03

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

**HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

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/s/

Eric Bastings
9/25/03 03:07:56 PM

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NDA 21-450

AstraZeneca Pharmaceuticals LP
Attention: Ms. Judy W. Firor
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

*Re: Request for a Waiver for Certain Post-Marketing Reporting Responsibilities
Under 21 CFR 314.80*

Dear Ms. Firor:

In your letter dated December 4, 2003, AstraZeneca Pharmaceuticals LP, U.S. agent for IPR Pharmaceuticals, Inc., requested waivers of certain post-marketing periodic safety reporting responsibilities under 21 CFR 314.80 for NDA 21-450 Zomig (zolmitriptan) Nasal Spray. You requested, under 21 CFR 314.90(a), a waiver from the requirement to submit to the Food and Drug Administration (FDA), as part of your post-marketing periodic safety reporting responsibilities, FDA form 3500A for each adverse experience that is determined to be both nonserious and expected. In addition, you have proposed that, in lieu of the format and timing of a periodic adverse drug experience report as required under our present regulations at 21 CFR 314.80(c)(2), you submit your annual international Periodic Safety Update Report (PSUR) that combines safety information for all dosage forms of Zomig, including tablets, orally disintegrating tablets, and nasal spray. The data lock point for this PSUR is based on the international birth date of the product, March 7, 1997.

Based upon the proposals stated in your letter, I concur that certain modifications in your post-marketing periodic safety reporting requirements are warranted at this time for the following product:

NDA 21-450 Zomig (zolmitriptan) Nasal Spray

Therefore, as of the date of this letter, the following waiver is granted for the above-listed NDA, as per 21 CFR 314.90(b):

For the above listed NDA, you may substitute your international Periodic Safety Update Report (PSUR) for the periodic adverse drug experience report required and described at 21 CFR 314.80(c)(2) provided all six of the following conditions are met:

- (1) the PSUR is prepared according to the guideline developed by the International Conference on Harmonisation (ICH) designated as ICH-E2C and published in the Federal Register on 19 May 1997 [62 FR 27470].

- (2) the PSUR is submitted on an annual basis based on the international birth date (IBD) of the product or moiety in the NDA (i.e., March 7, 1997). It is our understanding that you will lock your database annually on the month and day of the IBD in order to prepare the PSUR. You would then submit the final PSUR to us within 60 days of this data lock point as outlined in your letter. Please let me know if we have a misunderstanding about the timing of your report. Please note that you may generally combine all dosage forms and formulations of this moiety, as well as indications, in one PSUR. However, when you do so, you must submit one copy of the PSUR to each of your approved NDAs whose product is covered in the PSUR as well as a single copy of the PSUR for CDER's Office of Drug Safety to

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266.

- (3) while you may generally combine all dosage forms and formulations, as well as indications, in one PSUR, you separate into specific sections of the report the information on different dosage forms, formulations, and/or indications when such separation is needed to accurately portray the safety profile of the specific product (e.g., one should not combine, for example, information from ophthalmic drop dosage forms and solid oral dosage forms).
- (4) you attach, as an appendix to the international PSUR, copies of the 3500A forms that you are required to submit as part of a periodic safety report under 21 CFR 314.80(c)(2) (they may be submitted electronically; see <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm>). These include both medically confirmed and medically unconfirmed (consumer) reports. In addition, you are waived of the requirement to attach 3500As for individual safety reports for experiences that are determined to be non-serious and appear in the current labeling for the drug product. You should maintain records of these nonserious, labeled adverse experiences in your corporate drug product safety files. FDA does reserve the right to request these 3500As for the non-serious, labeled individual reports and expects that you would send them to us within five calendar days of such a request in the future. Information on these adverse experiences should be submitted in the section that includes a summary tabulation by body system of all adverse experience terms and counts of occurrences submitted during the reporting period.
- (5) you attach, as an appendix to the international PSUR, a tabular listing by body system of all consumer-reported adverse experience terms and counts of occurrences for individual safety cases, if such cases are not already included in the international PSUR tabular listings. If not included in other listings, these

lists should be segregated by classification of report (e.g., serious/unexpected; serious/expected; non-serious/unlisted; and non-serious/listed).

- (6) you attach, as an appendix to the international PSUR, a narrative that references the changes, if any, that you believe appropriate, based on the new information received in the reporting period, in your approved U.S. labeling for the product(s) covered by the PSUR. In this appendix, please also include a copy of the most recently approved U.S. labeling for the product(s) covered by the PSUR.

The waiver outlined in this letter will be in effect until you are notified in writing that it has been discontinued. Also, please note that this waiver in no way affects your other reporting responsibilities under 21 CFR except as specifically outlined in this letter (e.g., this waiver does not affect your expedited reporting responsibilities for suspected adverse reactions that are serious and unlabeled).

If you have any questions about this waiver, please do not hesitate to contact me at (301) 827-3219.

Sincerely,

{See appended electronic signature page}

Paul J. Seligman, M.D., M.P.H.
Acting Director
Office of Drug Safety
Director
Office of Pharmacoepidemiology and Statistical Science
Center for Drug Evaluation and Research

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/s/

Paul Seligman
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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Chen, Lana Y

From: Oliva, Armando
Sent: Tuesday, August 12, 2003 2:22
To: Chen, Lana Y
Cc: Prohaska, Kevin
Subject: Zomig NS labeling.doc

Lana, here is the labeling for the action package. The highlighted changes are those that differ from the approvable labeling that we issued last winter. The sponsor has agreed to all of these changes.

I'll send you my team leader memo shortly. Please put together the action package. The approval letter should contain the following language:

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28 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



MEMORANDUM

Date: August 12, 2003
From: Armando Oliva, MD
To: Russell Katz, MD, Division Director, DNDP
Subject: NDA 21-450; Zomig Nasal Spray

The sponsor proposes to market an intranasal formulation of zolmitriptan for the treatment of acute migraine. Zolmitriptan currently is marketed as an oral tablet (2.5mg, 5mg) and as an orally disintegrating tablet (2.5mg, 5mg). The submission addressed in the memo is the response to the approvable letter issued 12/19/02 for the original Zomig Nasal Spray NDA. Dr. Kevin Prohaska provides the clinical review and Dr. Yong-Cheng Wang provides the biometrics review.

The original application contained the results from a single randomized controlled trial (hereafter trial 077) which demonstrated efficacy of the nasal spray at doses of _____ 5mg. Long-term safety was supported by the results of two long-term safety studies (078 and 122). The sponsor proposes to market _____ doses: _____ 5mg.

The main issue precluding approval of the nasal spray was that the efficacy study was conducted using a clinical device, yet the to-be-marketed device was slightly different and it failed to show *in vitro* equivalence to the clinical device. I refer the reader to the approvable letter, which clearly outlines those deficiencies. Several of the *in vitro* bioequivalence parameters were outside the acceptable limits.

The approvable letter suggested three options to address this deficiency:

1. Repeat the *in vitro* testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.
2. Provide *in vivo* pharmacokinetic data to demonstrate bioequivalence.
3. Provide efficacy data from a well designed, randomized controlled trial.

The sponsor has chosen option #3 and provides efficacy data from an interim analysis of an ongoing randomized controlled trial (hereafter 022) that uses the to-be-marketed spray device. We agreed to such an approach in a teleconference dated 2/11/03.

Study 022 is an ongoing, large (N=1384), multicenter, randomized, placebo-controlled study that evaluates the early efficacy (15 minutes) of zolmitriptan nasal spray (ZNS) 5mg for acute migraine. We realize that this study is only capable of demonstrating efficacy of the 5mg to-be-marketed device (since it is the only dose being studied) —

[

]

Safety data in this submission consist of four open-label PK studies (001, 002, 110, 124) and blinded data from the ongoing 022 study and another study (120). No new safety concerns arise from these data, given the limitations of blinded data. I refer the reader to Dr. Prohaska's review for details and I do not discuss these data further in this memo.

Study 022 plans to enroll 1592 subjects to achieve 1384 evaluable patients to compare the efficacy of ZNS 5mg vs. placebo using the early primary endpoint of headache response at 15 minutes. The study permits treatment of up to two migraines with study medication. The study had a typical design for migraine studies of this type. I refer the reader to Dr. Prohaska's review for study design details. In summary, randomized IHS-defined migraine patients treated a moderate or severe migraine headache with study medication and recorded subjective efficacy measurements at pre-specified time points post-dosing. The primary endpoint for the interim analysis was pre-specified as the headache response at 2 hours, defined as a decrease in pain intensity to mild or none at the 2 hour time point, using data from the first attack only.

The interim analysis presented here evaluates the headache response at 2 hours in the first 210 patients from this study. This analysis plan was submitted for review on 2/28/03, and uses an alpha spending function methodology to preserve the overall type I error of the experiment (see statistical review for additional details). The interim analysis was tested at a significance level of 0.0027, and the final analysis will be tested at 0.0479.

The primary efficacy analysis for interim data is shown in Table 1 (taken from the medical review, page 6, and the statistical review, page 5). It employed logistic regression using treatment, region, and baseline intensity in the model. It shows a 70% 2 hour response rate for ZNS 5mg vs. 47% for placebo. This was highly statistically significant.¹

Table 1: Study 022 – Interim Primary Efficacy Results – 2-HR Headache Response

Population	Zomig NS		Placebo		p-value
	N	Headache Response (%)	N*	Headache Response (%)	
ITT – Sponsor	108	76 (70.4)	100	47 (47)	0.0005
ITT – FDA (Dr. Wang)	108	76 (70.4)	102	48 (47)	0.0006

* The discrepancy in the placebo group resulted from the fact that the sponsor did not include two placebo patients in the analysis: one had missing data at 2 hours, and the other had taken escape medication before 2 hours when migraine headache pain was mild. Dr. Wang included these two patients using an LOCF approach for missing data.

¹ Of note, the response rate for ZNS 5mg is numerically similar to that seen in the earlier efficacy trial that used the 5mg clinical device (70% now vs. 69%, table 2 page 3 of my team leader memo for the original NDA). The placebo response rate from that study was lower, 31%, compared to 47% in this trial. Due to the difference placebo response rates in the two studies, this results in a larger observed treatment effect for the clinical device (38%) vs. the to-be-marketed device (29%).

The sponsor's analysis failed to demonstrate superiority over placebo with regard to nausea, photophobia, and phonophobia in those patients who reported these symptoms at baseline (this despite the fact that numerically results were similar in study 077, which did demonstrate superiority on the secondary symptoms. Once again, a higher placebo response rates in study 022 was largely responsible for the lack of significance).

The Division's preferred analysis of these endpoints looks at the prevalence of these symptoms at 2 hours (Table 2, taken from the biostatistical review, Table 6, page 14). These analyses demonstrate a nominally significant advantage of ZNS 5mg over placebo with regard to photophobia at 2 hours ($p=0.03$) and numerical trends for photophobia ($p=0.17$) and nausea ($p=0.08$).² If one tests these using the same level of significance for this interim analysis that was used for the primary analysis (0.0027), then none of these analyses are positive.

Table 2: Study 022 – Associated Symptoms at Two Hours

	ZNS 5.0 mg (N = 108) ^a	Placebo (N = 102)
Nausea		
Patients with associated symptom at 2 h (%) ^b	19 (18.6)	28 (27.7)
p-value ^c	0.080	NA
Photophobia		
Patients with associated symptom at 2 h (%) ^b	37 (34.3)	50 (49.5)
p-value ^c	0.026	NA
Phonophobia		
Patients with associated symptom at 2 h (%) ^b	29 (26.9)	36 (35.6)
p-value ^c	0.170	NA

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

^a Patients received trial medication and treated a migraine attack.

^b Headache response is as a reduction in headache intensity from moderate or severe to mild or none.

^c P-value is calculated by chi-square test.

^d Odds ratio and 95% confidence limits (CI) are estimated by SAS FREQ procedure.

² The first efficacy study (077) demonstrated nominal significance of ZNS 5mg at 2 hours on all three migraine-associated symptoms: nausea, photophobia, and phonophobia. Absolute prevalences of these symptoms at 2 hours were similar across the two studies (see table below, taken from my team leader memo, table 3, page 5). Lower placebo prevalence rates in study 022 (and perhaps the smaller sample size - N=108 for 022 vs. N=236 for 077 for the 5mg group) contributed to the lack of nominal significance.

Table Error! Main Document Only.: Study 0077 – Prevalence of Associated Symptoms at 2 Hours

	ZNS 5.0 mg (N=236)	ZNS 2.5 mg (N=224)	ZNS 1.0 mg (N=236)	ZNS 0.5 mg (N=226)	Zolmitriptan Tab 2.5 mg (N=232)	Placebo (N=226)
Nausea (%, p-value)	59 (25.1) <0.01	67 (29.9) 0.11	71 (30.3) 0.13	76 (34.4) 0.56	75 (32.9) .35	83 (37.1)
Photophobia (%, p-value)	75 (31.9) <0.01	92 (41.3) <0.01	103 (44.2) <0.01	111 (50.2) 0.03	91 (39.7) <0.01	136 (60.7)
Phonophobia (%, p-value)	61 (26.0) <0.01	62 (27.8) <0.01	83 (35.6) <0.01	90 (40.9) 0.06	69 (30.4) <0.01	111 (49.8)

Discussion

The results of the previous study (077) demonstrated the efficacy of zolmitriptan when administered with the device used in that study (clinical device). The interim analysis of study 022 was conducted to demonstrate efficacy of zolmitriptan 5mg when administered with the to-be-marketed device. This analysis demonstrates efficacy against migraine pain using the traditional two-hour headache response rates (70% vs. 47%, $p=0.0006$). The interim analysis failed to demonstrate efficacy against the three key secondary associated symptoms of nausea, photophobia, and phonophobia when one tests these using the same level of significance (0.0027) used for the primary analysis. Even when one uses a nominal significance of 0.05, the analysis fails on nausea and phonophobia.

It is interesting to note that the headache response rates for ZNS 5mg in both studies were essentially identical (69% vs. 70% for studies 077 and 022, respectively), and the prevalence of the three key associated symptoms were quite similar at two hours in both studies. Furthermore, in study 077, ZNS 5mg did "win" on the three key secondary analyses. However, the placebo group did inexplicably better, on all 4 measures of migraine efficacy, in study 022 compared to study 077, resulting in smaller treatment effects across all 4 endpoints in the study currently under review. How does one interpret these results?

We have long held the position that an effective migraine treatment must demonstrate efficacy on the four key migraine symptoms of pain, nausea, photophobia, and phonophobia. Even though the latter three are termed "secondary" endpoints in typical migraine protocols, they are, for all practical reasons, co-primary endpoints along with pain. These criteria for approval has been applied to all recent approvals of acute migraine treatments, both in this Division and in the Division of Over The Counter Drug Products. However, we have also approved *lower* doses of a formulation that failed to win on all 4 endpoints, provided it won on at least pain and provided that a *higher* dose did win all on all four (and thereby establishing its efficacy as a migraine treatment). We have never, to my knowledge, approved a formulation where even the highest planned marketed dose fails to win on all 4 endpoints.

Clearly, if zolmitriptan had never been approved (*i.e.*, the molecule had never been established as effective against all four symptoms of migraine), then the interim results of study 022 fail to demonstrate the efficacy zolmitriptan as a treatment for migraine. However, we have ample evidence from other formulations that zolmitriptan, the molecule, is an effective treatment for migraine.

We have, to my knowledge, never approved a new formulation of an already-approved migraine product that didn't win on all four key symptoms at least at the highest dose. In other words, we know that zolmitriptan is an effective migraine treatment when given orally, but it is an effective migraine treatment when given intranasally? Clearly, the answer is yes if it is administered using the clinical device. When administered with the to-be-marketed device, all we can say at this point is that it is effective against pain only, although numerically it trends in the proper direction on the other three symptoms.

In my mind, the key question upon which approvability of this application rests is whether we should require that a new formulation (of an already approved migraine treatment) win on all four key migraine symptoms. I think the answer is no, but it must win on pain, which is for most migraine sufferers the most disabling symptom.

The reason I conclude this is because we already accept the fact that a lower dose of an existing formulation doesn't necessarily have to win on all four symptoms as long as it wins on pain. We can therefore view the intranasal formulation, at worse, as a "lower dose equivalent" of the tablet which is, at the very least, effective against pain. At best, they are similar but we don't know this due to lack of power in this study, or some other factor. The positive trend in the other three symptoms is reassuring.

For this reason, I conclude that we should approve Zolmitriptan 5mg Nasal Spray.

This creates an unusual situation where only the high dose of a formulation is approved

This is a safety concern because lower doses, that are likely safer, are not available. I believe this concern is minor, given the fact that systemic exposure to a 5mg nasal spray dose is analogous to a 5mg oral dose, which is known to be reasonably safe, and the labeling directs prescribers and users to use the oral formulations in order to achieve a lower dose.

In summary, I recommend approval of Zolmitriptan 5 mg Nasal Spray with the corresponding labeling that is attached to the action package.

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling



Date: **MAR 27 2003**

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 120, Room No. 4049
Woodmont Building II
1451 Rockville Pike
Rockville, MD 20852-1448

RE: NDA 21-450
ZOMIG[®] (zolmitriptan) Nasal Spray
Complete Response to December 19, 2002 Approvable Letter

Dear Dr. Katz:

Reference is made to the December 19, 2002 Approvable Letter issued to AstraZeneca Pharmaceuticals LP (AstraZeneca) for NDA 21-450, ZOMIG[®] (zolmitriptan) Nasal Spray and our December 20, 2002 Intent to File an Amendment Letter. Contained herein is a complete response to the December 19, 2002 Approvable Letter.

The Approvable Letter cited one single deficiency. Reference is also made to the February 11, 2003 teleconference held between FDA and AstraZeneca personnel to discuss options to address the deficiency. An agreement was reached that an Interim Analysis for a clinical trial entitled: "A Multicenter, Randomized, Placebo-controlled, Double-blind, Parallel-group Trial to Evaluate Early Efficacy and Tolerability of zolmitriptan (ZOMIG[®]) Nasal Spray in the Acute Treatment of Adult Subjects with Migraine" (311CUS/0022) would fulfill the aforementioned deficiency and gain approval of the ZOMIG[®] (zolmitriptan) Nasal Spray 5mg strength.

The complete response to the December 19, 2002 Approvable Letter consists of the following:

- An Interim Analysis of Efficacy Data for Trial 311CUS/0022
- A Safety Update Report for ZOMIG (zolmitriptan) Nasal Spray
- Revised Draft Labeling

A brief summary of each of these three components follows:

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Interim Analysis

Presented herein is the Interim Analysis of Efficacy Data for Trial 311CUS/0022. The Interim Analysis used validated, unblinded efficacy data from a subset of 210 patients who treated the first migraine headache attack with study medication. The data were analyzed using the 2-hour headache response of the first treated attack as the primary endpoint. This sample size provided adequate power (for 2-hour headache response) to show superiority over placebo and confirm the clinical equivalence of the 2 nasal spray devices ("commercial" and "clinical").

The Interim Analysis shows that zolmitriptan 5-mg nasal spray was more efficacious than placebo in the treatment of migraine headache with or without aura in adults. Statistical superiority of zolmitriptan was found for the primary endpoint of 2-hour headache response when compared with placebo according to the prespecified Interim Analysis significance boundary of 0.0027. (The plan for the adjustment on the overall type I error due to the addition of this Interim Analysis for Trial 311CUS/0022 was provided to Ms. Lana Chen of your Office via an email from Mr. Matthew Arnold of AstraZeneca on February 28, 2003. A hard copy of this summary was additionally submitted to NDA 21-450 on March 26, 2003.) The zolmitriptan 5-mg nasal spray group also achieved numerical superiority for headache response at the earlier and later timepoints. The headache response increased consistently at all timepoints from 15 minutes to 4 hours. In the subset of patients with migraine-associated symptoms at baseline, the resolution of nausea, phonophobia, and photophobia occurred at numerically higher rates in the zolmitriptan 5-mg nasal spray group for all 3 symptoms at 2 hours. This separation from placebo did not achieve statistical significance; however, the sample sizes were small. These data show superiority to placebo as prospectively defined in the Interim Analysis plan and, therefore, demonstrate the efficacy of the zolmitriptan 5-mg commercial nasal spray device.

Note: Financial Disclosure and Debarment information are not presented for Trial 311CUS/0022 in the Interim Analysis. They will however be presented in the final Clinical Study Report upon completion of Trial 311CUS/0022.

Safety Update Report

As specified in the Approvable Letter, a Safety Update Report (SUR) for ZOMIG (zolmitriptan) Nasal Spray was performed and is presented herein.

This SUR provides additional safety data from the clinical trial program for zolmitriptan nasal spray collected since the 4-month safety update (submitted to FDA on June 27, 2002) up to the data cutoff date of December 31, 2002. Data in this report include new safety findings from 4 completed pharmacokinetic studies: SA-ZOB-0001, SA-ZOB-0002, 311CJP/0110, and 311CIL/0124 and 2 ongoing, blinded, placebo-controlled efficacy and tolerability studies (Studies 311CUS/0022 and 311CIL/0120). Overall, new safety data is presented from 121 patients in the 4 pharmacokinetic studies and 1170 patients from the two blinded, placebo-controlled studies.

Zolmitriptan nasal spray 5.0 mg was shown to be well tolerated in the clinical pharmacology and placebo-controlled, blinded studies presented in this SUR with no clinically significant differences from previously reported data at the 5.0 mg nasal spray dose. Serious adverse events (drug-related and non-drug-related) were rare. Very few adverse events led to patient withdrawal from therapy. Adverse events of all types, including nasopharyngeal adverse events, were typically mild-to-moderate, transient, and resolved without intervention. The types of adverse events seen were mainly known pharmacological effects of triptans (ie, paresthesia) or typical of drugs administered via the nasal route (ie dysgeusia), and were consistent with those seen before in the zolmitriptan clinical development.

Labeling

The Approvable Letter included FDA revised draft labeling with annotations that required further clarification or editing. AstraZeneca has accepted all of the Agency's comments and provided additional information for statements where requested. AstraZeneca has reformatted the Patient Information Leaflet into a question and answer format in accordance with the Agency's request. AstraZeneca used the current Relpax® Patient Information Leaflet as a guide for this reformatting as we believe this to represent the Agency's current thinking.

The Approvable Letter presented an additional comment concerning the zolmitriptan drug substance specification. AstraZeneca had previously received this comment in a December 13, 2002 email from Ms. Lana Chen of your office to Mr. Matthew Arnold of AstraZeneca. AstraZeneca had addressed this comment in our December 17, 2002 submission to NDA 21-450.

AstraZeneca believes that the information contained herein represents a complete response to the December 19, 2002 Approvable Letter and looks forward towards the continued cooperation in obtaining approval of the ZOMIG® (zolmitriptan) Nasal Spray NDA.

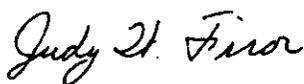
The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-450: ZOMIG® (zolmitriptan) Nasal Spray

Please direct any questions or requests for additional information to me, or in my absence, to Matthew E. Arnold, Regulatory Project Manager, at (302) 886-3303.

Sincerely,



Judy W. Firor
Regulatory Affairs Director
Regulatory Affairs
Telephone: (302) 886-7539
Fax: (302) 886-2822

JWF/mea

Enclosure

Technical Review Jacket: Ms. Lana Chen, HFD-No. 120, Room 4031 (Cover Letter Only)

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37 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEMORANDUM

DATE: December 16, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-450

SUBJECT: Action Memo for NDA 21-450, for the use of Zomig (zolmitriptan) Nasal Spray for the acute treatment of migraine

NDA 21-450, for the use of Zomig (zolmitriptan) Nasal Spray for the acute treatment of migraine, was submitted by AstraZeneca Pharmaceuticals LP on 3/6/02. Zomig tablets are already approved for the same indication. This application contains the results of a single, randomized controlled trial examining Zomig NS doses 0.5 mg, 1 mg, 2.5 mg, and 5 mg compared to Zomig tablet, 2.5 mg, and placebo. It also contains the results of open, uncontrolled safety data.

In addition, it contains CMC information, as well as biopharmaceutic data, including data on the performance of the device used in the controlled trial (and in much of the long-term safety data) and the device the sponsor intends to market.

The application has been reviewed by Dr. Kevin Prohaska, medical officer (review dated 12/10/02), Dr. Yong-Cheng Wang, statistician (review dated 11/20/02), Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/7/02), Dr. Martha Heimann, chemist (review dated 12/13/02), and Dr. Armando Oliva, Neurology Team Leader (memo dated 12/12/02).

Dr. Prohaska recommends that the application be approved, while Dr. Oliva recommends that the division find the application Not Approvable. Dr. Jackson finds the application unacceptable. I will briefly review the relevant findings and provide the rationale for the Division's action.

As Drs. Oliva, Prohaska, and Wang conclude, the single controlled trial establishes that Zomig NS is effective as an acute treatment for migraine. I agree with the clinical team that all doses studied have been shown to be effective. It is worth noting, as does Dr. Oliva, that the only dose in which there were statistically significant between-treatment differences for all 3 "secondary" outcomes (nausea, photophobia, phonophobia) was the 5 mg dose; there were no other significant contrasts for the nausea variable (including the zolmitriptan 2.5 mg tablet). As Dr. Oliva notes, it has been our policy to approve treatments for a specific migraine indication only when there are significant between-treatment differences on all 4 primary symptoms (headache and the 3 symptoms

noted above). However, I agree with Dr. Oliva that this study provides sufficient evidence to conclude that Zomig NS is effective, as we define that term, as a treatment for acute migraine (it is also worth pointing out that the approved Zomig 2.5 mg tablet was not significantly different from placebo for nausea; this, of course, does not establish the nasal spray's efficacy against this symptom, only that the study did not have assay sensitivity for this outcome).

As the reviewers note, the trial examined the effects of drug on 3 consecutive headaches, but our analyses were limited to the first treated headache for each patient. In addition, there were no significant safety findings beyond those already known for Zomig tablets, except for symptoms related to the route of administration (including throat symptoms and epistaxis). The review team concludes, and I agree, that the clinical data establish the safety and effectiveness of zolmitriptan given intranasally.

However, as Dr. Jackson notes, the to-be-marketed spray device is not equivalent to the clinically studied device on a number of required in vitro performance measures. In particular, all doses, _____, fail one or more equivalence criteria (see, for example, his review, pages 1-2).

We discussed these failures with the sponsor in a phone call on 10/9/02. On 11/1/02, the sponsor made a submission that purported to address our concerns.

In this submission, the sponsor argued that the equivalence criteria are inconsistent with industry standards, and that the failures were as the result of chance/variation. Dr. Jackson finds these arguments inadequate, and I agree.

The sponsor has also argued that the clinical data establish that the two devices are clinically equivalent. Dr. Oliva outlines their argument in detail. In brief, when patients completed the controlled trial, they were randomized (in a blinded fashion) to Zomig NS _____ 5 mg to treat subsequent headaches with the clinically studied device. When the controlled trial results became known, all patients were treated with 5 mg, given with the to-be-marketed device.

The firm argues that the patients who received the 5 mg dose after the controlled trial (with the clinically studied device) had similar response rates to the patients treated with 5 mg after all the patients were switched to this dose (given with the to-be-marketed device). Further, patients not randomized to the 5 mg dose after the trial had improved response rates once they were switched to the 5 mg to-be-marketed device. Finally, the response rates once all patients were switched to the to-be-marketed 5 mg dose were comparable to the rates in the 5 mg dose group from the controlled trial.

Dr. Oliva finds these arguments wanting, as do I.

I agree with him that it is inappropriate to make cross-study comparisons, as it is, in this case, inappropriate to compare response rates from the various phases of the extension trial, primarily for the reasons he cites (investigators knew when the switch to the 5 mg to-be marketed device was made, and it is generally known that estimates of treatment effects generally increase when all parties are aware that patients are receiving active doses [i.e., there is no placebo]).

For these reasons, then, I agree with Drs. Oliva and Jackson that the application cannot be approved at this time (Dr. Heimann recommends that the application be approved from the CMC perspective). I further agree that the application cannot be approved until the sponsor can produce evidence that the two devices are clinically equivalent. They can do this by performing additional in vitro tests (using, for instance, mechanical actuation), or by performing an in vivo equivalence study (of course, as Dr. Oliva recommends, they may also perform a controlled trial with the to-be-marketed device).

However, I do believe that the application can be considered Approvable, because the sponsor has demonstrated the safety and effectiveness of the product given intranasally.

For this reason, then, I will issue the attached Approvable letter with appended labeling.

Russell Katz, M.D.

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ON ORIGINAL

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

/s/

Russell Katz
12/19/02 10:32:55 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM**

Date: December 12, 2002
From: Armando Oliva, MD
To: Russell Katz, MD, Division Director, DNDP
Subject: NDA 21-450; Zomig Nasal Spray

This NDA provides information to support the approval of a new nasal spray formulation of zolmitriptan (Zomig Nasal Spray, Zomig NS or ZNS).

The application contains the results of a single efficacy study (0077) and data from two long-term studies (0078 and 0122, the latter was ongoing at the time of submission), as well as 5 PK studies involving healthy volunteers. The application also contains CMC and pharm/tox data.

Dr. Prohaska provides the clinical review, and Dr. Jackson provides the OCPB review. Dr. Wang provides the biostatistical review. Dr. Fossom and Dr. Heimann provide the pharm/tox and chemistry reviews, respectively, both of whom do not have any issues that would affect the approvability of the product. As a result, I do not discuss the chemistry or pharm/tox reviews in this memo.

Efficacy

Study 0077 was an international, randomized, double-blind, placebo-controlled, double-dummy, parallel group trial that compared 4 doses of ZNS (0.5mg, 1mg, 2.5mg, 5mg) with placebo and Zomig 2.5mg conventional tablets.¹ Eligible subjects were male or non-pregnant females, 18-65 years old, with an established (≥ 1 year) diagnosis of migraine with or without aura (IHS criteria) prior to the age of 50. They were to have 1-6 migraines per month in the two preceding months. Subjects with basilar, ophthalmoplegic, or hemiplegic migraine were excluded, as were those with serious medical conditions, and those with frequent non-migraine headaches.

After randomization, subjects were given sufficient medication to treat three migraine attacks, each with a single dose of medication, within a three-month period. Escape medication was permitted after two hours for severe pain, but discouraged until four hours post-treatment. Those who completed the trial were offered enrollment in the long-term safety trial (0078). Planned assessments occurred at 15, 30, 45, 60, 120, and 240 minutes.

¹ Of note, the study was conducted entirely outside the IND while the IND was on hold for pre-clinical issues. Although it does not appear that subjects were informed that the IND was on hold in the U.S., Dr. Fossom, the pharm/tox reviewer, believes that the original review of the pharm/tox data leading to a hold was faulty. The hold was lifted prior to NDA filing. Therefore, Dr. Prohaska believes that there are no ethical concerns in accepting the data and I agree (see section 5.3, page 22 of the medical review for more details).

The primary efficacy endpoint was the headache response at 2 hours, defined in the traditional manner (moderate or severe headache at baseline and mild or no headache at 2 hours). The analysis plan called for the use of a generalized linear mixed models using a step-down approach by comparing the doses of ZNS with placebo starting with the highest dose. Secondary outcome measures included measurement of the key secondary migraine symptoms (nausea, photophobia, phonophobia) at various time points.

A total of 1547 subjects were randomized and 1383 took at least one dose of study medication (the safety population). The sponsor's ITT population consisted of 1371 subjects. Their ITT definition include all subjects who treated a moderate to severe migraine and had at least one post-treatment efficacy follow-up. They excluded those who had a mild migraine at baseline. We normally include them in the analysis and count them as treatment failures (since they don't meet the definition of a responder: one who has moderate/severe pain at baseline AND mild/no pain at 2 hours). Dr. Prohaska included these 12 in his analysis (ITT_{Agency}) and the results and conclusions are unchanged.

The sponsor used data from the first 2 attacks in their analyses, whereas we traditionally accept only data from attack 1.² Table 1 (taken from the medical review, table 4, page 28) describes the various study populations used for analysis.

Table 1: Study 0077 – Study Populations for 1st Attack

Cohort	Randomized	Treated (Safety)	ITT _{Agency}	ITT	Per-Protocol
ZNS 5.0 mg	259	236	236	235	220
ZNS 2.5 mg	259	224	224	224	217
ZNS 1.0 mg	258	238	238	236	215
ZNS 0.5 mg	256	224	224	221	211
Zolmitriptan Tablet 2.5 mg	256	233	233	230	206
Placebo	259	228	228	225	213
Total	1547	1383	1383	1371	1282

Subjects in each treatment group were generally balanced with regards to baseline demographic information (medical review, table 7, page 30), and baseline migraine characteristics with the exception of baseline headache intensity (ZNS 5mg – 16.6% severe and ZNS 0.5mg – 28.1% severe).

² They originally planned to use data from all three attacks, but noted that medication use for attack 3 was dependent on treatment assignment...i.e., subjects on higher doses were more likely to treat a third attack. For this reason, they excluded data from attack three. Since we rely on data from attack one only, this did not affect our analyses.

Although the 1st attack analysis was not the protocol-specified primary analysis, the sponsor did perform that analysis, which I present here, along with the corresponding agency's analyses (medical review, table 9, page 32).

Table 2: Study 0077 – Headache Response at 2 Hours

	ZNS 5.0 mg (N=235)	ZNS 2.5 mg (N=224)	ZNS 1.0 mg (N=236)	ZNS 0.5 mg (N=221)	Zolmitriptan Tab 2.5 mg (N=229)	Placebo (N=226)
Sponsor's Analysis (medical review, table 9, page 32)						
Patients with 2 hrs response (%)	157/228 (68.9)	121/219 (55.3)	137/232 (59.1)	86/217 (39.6)	133/220 (60.5)	67/218 (30.7)
Treatment comparison: ZNS dose vs. placebo						
Odds Ratio	5.13	3.05	3.47	1.60		
95% CI	(3.40, 7.73)	(2.04, 4.56)	(2.33, 5.17)	(1.07, 2.41)		
p-value	0.0001	0.0001	0.0001	0.0223		
Dr. Prohaska's Analysis (medical review, table 25, page 48)						
2HR Response Rate (%)	163/236 (69)	124/224 (55)	138/236 (58)	91/223 (41)	138/232 (60)	69/226 (31)
p-value	<0.01	<0.01	<0.01	0.03	<0.01	
Dr. Wang's Analysis (statistical review, table 5, page 9)						
2HR Response Rate (%)	157/228 (68.9)	121/219 (55.3)	137/232 (59.1)	86/217 (39.6)		67/218 (30.7)
p-value	<0.0001	<0.0001	<0.0001	0.053		

All doses of ZNS, according to the sponsor, were associated with significantly higher 2 hour headache responses compared with placebo. Although there was an imbalance in the proportion of patients reporting baseline severe pain, this was accounted for in the model used in the analysis. Dr. Wang obtained the exact same number of responders for each treatment group; however, the p-value for the 0.5mg group in Dr. Wang's analysis is 0.053, whereas the sponsor's p-value is 0.0223. This is because the sponsor included the Zolmitriptan 2.5mg tablet group in the model, which Dr. Wang believes is not appropriate and introduces bias. Dr. Wang's analysis excludes that group from the model.

Dr. Wang argues that there is no evidence of efficacy for the 0.5mg dose at 2 hours because the p-value of 0.053 is greater than 0.0125, using a Bonferroni adjustment for multiple comparisons. Dr. Wang notes in page 15 of the statistical review that the sponsor did not define any adjustment procedure for multiple comparisons. In fact, the sponsor *did* define a step-down procedure on page 39/7426 of the study report (il0077.pdf):

"In order to take account of the multiple testing of the treatment groups, a step-down approach was adopted by comparing the doses of zolmitriptan nasal spray with placebo starting from the highest dose. The intranasal 5.0 mg versus placebo contrast was tested first and if not significant at the 5% level then no further testing was undertaken."

[]

Various subgroup analyses (age, weight, gender, menses, baseline pain, migraine upon awakening, aura, nausea) suggested that efficacy was unaffected, with the exception of baseline pain (subjects with moderate pain had higher response rates than those with severe pain)

The sponsor looked at "improvement" (*i.e.*, resolution) of baseline nausea, photophobia, and phonophobia (and analysis which Dr. Wang also reproduced). This is not the traditional analysis that we like to see. We like to see the proportion of patients who have each symptom at 2 hours (since it includes the entire ITT population in the analysis and considers the possibility that some subjects develop the symptoms during treatment). Dr. Prohaska performed this analysis, which I present in Table 3 (adapted from table 27 in the medical review, page 50). The nominally significant results for ZNS are bolded for clarity.

Table 3: Study 0077 – Prevalence of Associated Symptoms at 2 Hours

	ZNS 5.0 mg (N=236)	ZNS 2.5 mg (N=224)	ZNS 1.0 mg (N=236)	ZNS 0.5 mg (N=226)	Zolmitriptan Tab 2.5 mg (N=232)	Placebo (N=226)
Nausea (%, p-value)	59 (25.1) <0.01	67 (29.9) 0.11	71 (30.3) 0.13	76 (34.4) 0.56	75 (32.9) .35	83 (37.1)
Photophobia (%, p-value)	75 (31.9) <0.01	92 (41.3) <0.01	103 (44.2) <0.01	111 (50.2) 0.03	91 (39.7) <0.01	136 (60.7)
Phonophobia (%, p-value)	61 (26.0) <0.01	62 (27.8) <0.01	83 (35.6) <0.01	90 (40.9) 0.06	69 (30.4) <0.01	111 (49.8)

The ZNS 5.0mg dose was nominally significantly better than placebo at two hours for all three associated symptoms. The other ZNS doses all failed on nausea (it's interesting that the zolmitriptan tablet dose also failed on nausea), although they were all in the right direction with evidence, at least numerically, of a dose response.

Since zolmitriptan has previously been shown to be an effective migraine treatment, the results seen for the 5.0mg dose (on pain, nausea, photophobia, and phonophobia) confirm that it is also an effective migraine treatment when given intranasally. We have not required that each dose be positive for all key secondary endpoints in order to approve that dose, but rather, at least one dose must "win" on all 4 endpoints (primary and 3 secondary) in order to demonstrate its effect as an anti-migraine treatment.

Safety

Dr. Prohaska provides a detailed review of the safety database contained in the NDA. The majority of the data comes from two long-term (one year) trials.

Study 0078 was the long-term extension of the pivotal efficacy trial, study 0077. Subjects who successfully completed 0077 were eligible to enroll in this study. The study had 2 phases. In the first phase, subjects were randomized to one of 4 doses of ZNS (0.5mg, 1mg, 2.5mg, 5mg) and allowed to treat all migraine attacks with a single dose of study medication. In phase 2, all subjects were switched to the 5mg dose (this was done after 0077 was analyzed and the 5mg dose was determined to be the best optimal dose). I discuss this trial in more detail in the next section of this memo when I discuss the pharmacokinetic issues associated with the different spray devices used during development.

Study 0122 used only the 5mg dose. Subjects again were permitted to treat every migraine with Zomig Nasal Spray. The one difference with this study is that re-treatment with a second dose of ZNS was permitted after 2 hours.

The development program achieved an adequate number of long-term exposures (see medical review, table 30, page 55). With data from the 4-month safety update, there were 475 subjects who treated 2 or more migraines for 6 months and 417 for one year.

In general, Dr. Prohaska concludes that the safety profile of ZNS appears to be similar to that of the approved zolmitriptan formulations (and other triptans) with the exception of nasopharyngeal symptoms.³ Nasopharyngeal discomfort and unusual taste were common, generally mild, and non-serious, and dose-related (for the 5mg dose, NP discomfort occurred in 3%, vs. 1.8% in placebo, and unusual taste occurred in 21% vs. 3% in placebo). A cohort of subjects in studies 0078 and 0122 (580 total) underwent nasopharyngeal examinations of one sort or another. Abnormalities were low (0.7%) and mild (infections, swollen turbinate, minor nasal ulcerations and evidence of minimal bleeding).

Clinical Pharmacology

The sponsor conducted 5 PK studies to evaluate the performance of Zomig Nasal Spray *in vivo*. These were 136-032, 311CIL/0041, 311CIL/0079, 311CIL/0102, and 311CIL/0104. These studies showed that after the administration of single and multiple doses (0.5mg, 1mg, 2.5mg, 5mg), the pharmacokinetics was dose proportional, that Zomig NS was primarily distributed to and absorbed by the nasopharynx region, that absorption and distribution of a 5mg dose was unaffected 30 minutes after a single dose of intranasal xylometazoline (a nasal decongestant) compared to ZNS 5mg alone.

The pharmacokinetics, metabolism, and elimination profiles are zolmitriptan when taken orally or intranasally are similar, and suggests that prescribing information relating to drug-drug interactions and drug-demographic interactions for Zomig tablets is equally relevant to the nasal spray formulation.

³ Nasopharyngeal symptoms and abnormal taste are also quite common with the other intranasal triptan formulation: Imitrex Nasal Spray.

During development, the sponsor changed the nasal spray device used to deliver Zomig Nasal Spray. The pivotal trial 0077 was conducted using the earlier "clinical" device, and the device intended for marketing ("commercial") device was introduced during the course of the long-term study 0078. The OCPB review focuses on the *in vitro* tests performed to attempt to show bioequivalence between these two devices. I refer the reader to Dr. Jackson's review for a detailed description of the two devices and the *in vitro* testing that was performed (figure 1, page 6 of his review illustrates the two devices).

The two devices are very similar. They are identical with regards to device firing mechanism and contact materials; however, the appearance of the outer body of the device has been modified to incorporate a safety feature preventing removal of the filled vial. A thumb push has also been added to ease firing, and the protection cap has been designed to prevent actuation of the device prior to patient use. *In vitro* testing was performed in accordance with the document: CDER Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, June 1999.

In summary, the sponsor measured various parameters: dose or spray content uniformity, droplet size distribution (), particle size distribution, drug and aggregate particle size density, spray pattern (Dmax, Dmin, Ovality), and plume geometry. Bioequivalence was based on demonstrating that the ratio of geometric means (test/reference) falls between — for all parameters.

Various *in vitro* tests had ratios for geometric means that exceeded these limits. These are summarized in Table 5 (adapted from the OCPB review, pages 32-33). Because of these deficiencies, OCPB cannot conclude that the two products are bioequivalent based on the *in vitro* testing alone.

Table 5: In vitro Comparison of the Commercial and Clinical Spray Devices

Parameter	Ratio geometric means
Particle Size	
┌	0.88
	0.89
	1.57
	1.82
	0.83
└	1.18
	1.18
Plume Geometry 5.0mg product	
Parameter-Length Value	
0° Beginning	0.81
0° Middle	0.79
0° End	0.72
90° Beginning	0.84
90° Middle	0.74
90° End	0.68
Parameter-Spray Angle Value	
0° Beginning	1.12
0° End	0.64
90° Beginning	1.19
90° End	0.71

Although the two devices have the same specifications for the actuation force, Dr. Jackson hypothesizes that “any combination of manual actuation differences and batch to batch variation of the break ring (which appears to be part of the pre-compression mechanism) could result in large variation in the median droplet size of particles delivered from study to study with different lots of the spray device.” (page 9 of the OCPB review).

In order to establish bioequivalence, OCPB recommends one of three possible options:

1. Repeat the *in vitro* testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.
2. Provide *in vivo* data to demonstrate bioequivalence
3. Provide efficacy data

We communicated the deficiencies of the *in vitro* testing in a teleconference with the sponsor on 10/9/02. They, in turn, responded in writing in a submission dated 11/11/02. That submission essentially contained two arguments: one using the existing *in vitro* data, and another based on clinical data from the long-term study 0078. Dr. Jackson reviewed

the *in vitro* argument (see his review dated 12/2/02). The sponsor argues either that the Agency standards are inconsistent with the industry standards (*i.e.*, the guidance document should not apply) or that the results are due to chance. Dr. Jackson concludes that the sponsor has provided no new data and no compelling new evidence to support the *in vitro* bioequivalence of the two products.

The clinical argument is somewhat complex, and requires a more detailed description of the long-term study 0078. This study had two parts. Subjects who successfully completed the randomized controlled trial 0077 were re-randomized in part 1 of study 0078 to receive, in a double-blinded manner, one of the four doses of ZNS (0.5mg, 1mg, 2.5mg, or 5mg) using the *clinical* device. There was no placebo group, so subjects and investigators knew that all were on active drug, but did not know the dose. Subjects were instructed to treat all migraine attacks with a single dose of study medication. Efficacy data for each attack were recorded and analyzed.

Once the results of study 0077 were available, the sponsor chose the most optimal dose (which in their estimation was the 5mg dose). At this point, all subjects still enrolled in 0078 were switched to the 5mg dose. This was the beginning of part 2 of the study and was exactly coincident with the switch to the *commercial* device (the sponsor confirmed this fact via email on 12/6/02). Investigators were aware that a switch to the best optimal dose would occur. Investigators also knew when the switch occurred (since new supplies of medication had to be shipped to the individual sites). Although the patient information leaflet did not specifically explain that a change in dose would or could occur, investigators certainly were free to inform them of this fact (although this was discouraged, according to the sponsor).

The sponsor argues that:

1. the two-hour response rates of all attacks treated by the 202 subjects in part 1 initially randomized to the 5mg clinical device were similar to the rates measured in the same patients using the commercial device in part 2.
2. Furthermore, there was a dose-response relationship shown in part 1 across the 4 dose groups suggesting that the study had assay sensitivity to detect a difference between two doses that were not equally efficacious.
3. Those not randomized to the 5mg dose in part 1 experienced an increase in response rates during part 2. The lack of a placebo arm is inconsequential since both parts 1 and parts 2 were double-blind to dose.
4. Finally, the response rates achieved with the 5mg commercial device in study 0078 are similar to the response rates achieved with the 5mg clinical device in study 0077.

As Dr. Prohaska points out, the cross-study comparison between 0078 and 0077 is not valid. Subjects in study 0078 were permitted to treat mild attacks, and this was not permitted in 0077. It is expected that subjects treating mild attacks will have higher response rates.

I don't believe it is appropriate to compare the results contained in part 2 with those obtained in part 1 because of potential biases resulting from the fact that investigators

knew (and could communicate to the subjects) that subjects were being switched to the best optimal dose. They also knew when this switch occurred, which was coincident with the change to the commercial device. This potential bias would, in my opinion, favor the commercial device. Furthermore, the results that the sponsor obtained come from the efficacy analysis across multiple attacks. We traditionally do not accept such analyses to demonstrate efficacy as we believe that a subject's experience with the study medication from a previous attack can influence the response rate for subsequent attacks. I conclude, as does Dr. Prohaska, that serious design issues preclude the acceptance of these data as evidence of efficacy of the commercial device.

Conclusion

In summary, I believe that Zomig NS when used with the clinical device is an effective treatment for acute migraine, but we don't have adequate evidence of bioequivalence between the commercial and clinical spray devices. I therefore recommend a non-approvable action. In order to address this deficiency, the sponsor must submit one of the following:

1. Repeat the *in vitro* testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.
2. Provide *in vivo* pharmacokinetic data to demonstrate bioequivalence. (We should remind the sponsor that C_{max} , AUC, and T_{max} should be bioequivalent, since a drug delivered via a commercial device that results in a longer T_{max} , compared to the T_{max} of the clinical device, may have an adverse effect on clinical efficacy for an acute migraine drug).
3. Provide efficacy data from a well-designed, randomized controlled trial.

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/s/

Armando Oliva
12/12/02 04:40:28 PM
MEDICAL OFFICER

APPEALS
GIC

Chen, Lana Y

From: Chen, Lana Y
Sent: Wednesday, October 02, 2002 2:55 PM
To: Matthew E Arnold (E-mail)
Cc: Chen, Lana Y
Subject: N 21-450: Statistical Requests

Matt,

Re: NDA 21-450 Zomig Nasal Spray

Please submit an additional efficacy analysis for nausea, photophobia and phonophobia at 2 hours (primary endpoint). Please submit the analysis results, data set and SAS program of the analysis. The analysis should be the comparison of zolmitriptan nasal spray vs. placebo for ITT population. If you have any questions, please let me know.

thanks,
Lana

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/s/

Lana Chen
10/3/02 10:46:57 AM
CSO

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Chen, Lana Y

From: Chen, Lana Y
Sent: Thursday, August 15, 2002 12:17 PM
To: Matthew E Arnold (E-mail)
Cc: Chen, Lana Y
Subject: N 21-450 Clarification

Matt,

In response to your request for clarification, please see the following from our Clinical Pharmacology and Biopharmaceutics team.

Question 1:

9a: Does the FDA want the % coefficient of variation for the reference data and the test data?

FDA Response: Yes

Question 2:

9b: Does the FDA want the mean of the log data for the reference data and the test data?

FDA Response: Yes

Question 3:

9c: Does the FDA want the \bar{c} within lot cv's for the reference data and the test data?

FDA Response: Yes

Question 4:

9d: Does the FDA want the calculations on the raw data or log data?

FDA Response: Raw data

Question 5:

9e: There are ~~lots of~~ \bar{c} data for the reference and test sets. How does the FDA want the ratio T/R calculated from the data? Does the FDA want the calculations on the raw data or log data?

FDA Response: Do calculations on raw and geometric means

Question 6:

9f: For the requested T-test, does the FDA want the calculations on the raw data or log data?

Additionally, our statistician feels that the F-test on the ratio of two variance (on log-scale) would be more appropriate than the T-test. Does the Agency agree that the sponsor should perform the F-Test on the data as opposed to the T-Test?

FDA Response: The FDA agrees with the firm that the F-test is appropriate for comparing 2 variances when the data are normal or transformed to be normal.

Question 7:

FDA Comment 11 ~~—————~~ You should provide for your aqueous nasal spray the amount of drug below ~~—————~~ for the clinical and commercial products. You should provide mass balance data for all studies for drug ex-actuation. You should provide raw ~~—————~~ data. Profile analysis of the impaction data are not needed.

FDA Response: The Guidance for Industry (June 1999 draft) under section V.A. suggests that the following batches are used:

- 1.pivotal clinical trial batch
- 2.primary stability batch
- 3.a production scale batch

Please let me know if you need any further clarification.

thanks,
Lana

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/s/

Lana Chen
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CSO

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Uppoor, Ramana S

From: Uppoor, Ramana S
Sent: Monday, April 15, 2002 5:28 PM
To: Chen, Lana Y
Cc: Uppoor, Ramana S; Fetterly, Gerald; Heimann, Martha R
Subject: re: Zornig nasal spray NDA

Hi Lana,

This e-mail is for the NDA file of Zornig nasal spray (NDA 21-450). Please appropriately document this. Ms. Pat Defayo from Astra Zeneca called me today to clarify the information request sent from us related to in vitro data for the intermediate strengths of this product. She clarified that only _____ 5 mg strengths are proposed to be marketed. She wanted to understand exactly what data is requested and I referred her to the draft guidance for nasal sprays and aerosols. _____

_____ The sponsor plans to submit this data latest by August of this year.

Ramana S. Uppoor

*Team Leader, Neuropharmacological Drug Products Team 2
Division of Pharmaceutical Evaluation I
Uppoorr@cdcr.fda.gov
301-594-5592*

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/s/

Ramana S. Uppoor
4/19/02 04:39:08 PM
BIOPHARMACEUTICS

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FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2858

Telecopier Cover Sheet

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DATE: April 8, 2002

DELIVER TO: Ms. Patricia DeFeo

Fax Number: (302) 886-2822

FROM: Lana Chen, R.Ph.
Regulatory Management Officer
Phone 301-594-5529

Total number of pages, including cover page: 2

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

Pat,

RE: NDA 21-450 Zomig Nasal Spray

Please see our requests attached.

Thanks,
Lana

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Statistical Requests:

1. SAS codes for the format library of all analysis datasets.
2. SAS codes for the primary efficacy results (table 6 - 9) and secondary efficacy results (table 10 - 24) in "Analysis of data from the 1st treated migraine attack in Trial 311CIL/0077".
3. SAS codes for the primary efficacy results (table 12 - 14) and secondary efficacy results (table 16 - 23) in the Multiple-attack Analysis.
4. Additionally, we have checked in EDR and have not found any protocol for the Trial 311CIL/0077. If you have submitted this protocol to FDA, please send a desk copy to:

Woodmont II
Attention: Yong-Cheng Wang, PhD (Statistical Reviewer)
1451 Rockville Pike
Rockville, MD 20852

If you have not submitted this protocol, please submit it ASAP.

Clinical Pharmacology Request:

We request that you provide *in vitro* data that evaluates equivalence of the clinical and to be marketed product for all intermediate strengths. Only data for the ~~5~~ 5 mg strengths have been submitted in the NDA. Abbreviated *in vitro* testing for the intermediate strengths is reasonable.

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/s/

Lana Chen
4/10/02 11:55:03 AM
CSO

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-450	Brand Name	Zomig Nasal Spray
OCPB Division (I, II, III)	I	Generic Name	Zolmitriptan
Medical Division	Neuropharmacology	Drug Class	Triptans
OCPB Reviewer	Gerald Fetterly, Ph.D.	Indication(s)	Migraine with or without auras in adults.
OCPB Team Leader	Ramana Uppoor, Ph.D.	Dosage Form	5 mg unit dose Nasal Spray
		Dosing Regimen	5 mg in 100 µl into one nostril
Date of Submission	2/27/02	Route of Administration	Intranasal
Estimated Due Date of OCPB Review	10/1/02	Sponsor	Astra Zeneca
PDUFA Due Date	12/27/02	Priority Classification	Standard
Division Due Date	11/1/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		Concomitant administration with vasoconstrictive decongestant to compare Bioavailability.
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X	3		Clinical Efficacy Trials
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Tablet as a reference for nasal spray
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS	X	1		Biowaiver based on in vitro BE data of Nasal Spray
BCS class				
III. Other CPB Studies				
Site of Absorption	X	1		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9		

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Background:		
<p>Zomig® is currently indicated for the treatment of migraine with or without auras in adults. The present formulations consist of a tablet and an orally disintegrating tablet. Following the onset of a migraine, several GI effects exist, such as nausea and vomiting, which could influence the absorption and onset of action of the tablet formulation. Thus, the sponsor has developed a Nasal spray solution for zolmitriptan in order to maximize the bioavailability of the drug through a different route of administration, with the belief that the onset of pharmacological action will be faster.</p> <p>In the current submission, the sponsor has performed 5 pharmacokinetic studies (#32, 41, 79, 102, and 104) to assess dose proportionality, single and multiple dose administration, the effect of pH on the absorption process through the nasal cavity, site of nasal absorption, and concomitant administration with a vasoconstrictive decongestant. Studies 32 and 41 used a _____ (pilot studies) and studies 79 and 102 used the _____ (pivotal studies). To assess efficacy and safety by the intranasal route, the sponsor has conducted three clinical trials, which utilized the same formulation and device _____ as in pivotal PK studies #79 and #102. The sponsor has changed the delivery device that is to be marketed compared with the device that was used in the clinical trials. Thus, the sponsor has conducted <i>in vitro</i> equivalence testing of the delivery device using _____ 5 mg strengths of zolmitriptan to support all dose strengths for marketing.</p>		
Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		1. We are requesting that the sponsor provide <i>in vitro</i> data that evaluates equivalence of the clinical and to be marketed product for all intermediate strengths. Only data for the _____ 5 mg strengths have been submitted in the NDA. Abbreviated <i>in vitro</i> testing for the intermediate strengths is reasonable.
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Are the clinical and to be marketed Nasal Spray products bioequivalent? 2. Can the sponsor be granted a biowaiver for the to be marketed device based on <i>in vitro</i> testing of the nasal spray? 3. Does a dose-response relationship exist for Zomig nasal spray? 4. Is the bioavailability of the nasal formulation similar to the tablet formulation?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-450, HFD-850(Lee), HFD-120 (Chen), HFD-860 (Fetterly, Upoor, Marroum, Mehta), CDR (Clin. Pharm./Biopharm.)

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/s/

Gerald Fetterly
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BIOPHARMACEUTICS

Ramana S. Uppoor
4/4/02 06:17:55 PM
BIOPHARMACEUTICS

APPLIED INC 401
2002-04-04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-450	Efficacy Supplement Type SE-	Supplement Number
Drug: Zomig (zolmitriptan) Nasal Spray		Applicant: AstraZeneca
RPM: Lana Chen, R.Ph.		HFD-120 Phone # 301-594-5529
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N 20-768 Zomig (zolmitriptan) Tablets N 20-231 Zomig -ZMT (zolmitriptan orally disintegrating tablets)
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		6 month= 9/28/03
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity Summary (approvals only)	See AP Pkg (Tab N)
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	See Tab M
• Original applicant-proposed labeling	See Tab M
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS/ODS email dated 11/21/02 in AE Pkg
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	See Tab M
• Applicant proposed	See Tab M
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	See Tab T
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See Tab K (AE Pkg)
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	2/18/00
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	See Tab P
❖ Clinical review(s) (indicate date for each review)	See Tab Q
❖ Microbiology (efficacy) review(s) (indicate date for each review)	See Tab V (AE Pkg)
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review Tab Q
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	See Tab O
❖ Statistical review(s) (indicate date for each review)	See Tab R
❖ Biopharmaceutical review(s) (indicate date for each review)	See Tab Q (11/7/02, 11/11/02) of AE Pkg
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	

CMC Information

❖ CMC review(s) (indicate date for each review)	See Tab S (12/13/02) of AE Pkg
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See Tab S (12/13/02) of AE Pkg
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	See Tab V (6/17/02) of AE Pkg
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	See Tab X of AE Pkg
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

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