

021450-Original-Approval-Pkg

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:  
21-450**

**Trade Name:** Zomig Nasal Spray

**Generic Name:** zolmitriptan

**Sponsor:** AstraZeneca Pharmaceuticals LP

**Approval Date:** September 30, 2003

**Indications:** For the acute treatment of migraine.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-450**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-450**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-450

Judy W. Firor  
US Regulatory Affairs  
AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
PO Box 8355  
Wilmington, DE 19850-8355

Dear Ms. Firor:

Please refer to your new drug application (NDA) dated March 27, 2003, received March 28, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zomig (zolmitriptan) Nasal Spray.

We acknowledge receipt of your submissions dated April 17, April 25, August 29, and September 30, 2003 .

The March 27, 2003 submission constituted a complete response to our December 19, 2002 action letter.

This new drug application provides for the use of Zomig (zolmitriptan) Nasal Spray for the acute treatment of migraine.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-450." Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your phase 4 commitment, as discussed in a teleconference held on August 28, 2003 and in your letter dated August 29, 2003, to provide the following information to support approval of (b)(4)----- spray devices.

1. The results of an open-label, randomized, two-period crossover bioequivalence study comparing two single 5 mg doses of zolmitriptan (ZOMIG®) administered to healthy volunteers in the two nasal spray devices used in the clinical development program. The study will assess the bioequivalence of the two devices after single dose administration of zolmitriptan to healthy volunteers with particular regard to AUC, C<sub>max</sub>, and t<sub>max</sub>. You commit to submit the results of this trial within 6 months of the date of this letter.
2. Additional data in support of the(b)(4)----- (details to be subsequently agreed to with the FDA) and to submit the-----he submission of the 5 mg bioequivalence study.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

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/s/

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Russell Katz  
9/30/03 12:40:35 PM

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-450**

**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-450

Judy W. Firor  
US Regulatory Affairs  
AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
PO Box 8355  
Wilmington, DE 19850-8355

Dear Ms. Firor:

Please refer to your new drug application (NDA) dated February 27, 2002, received February 27, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Zomig (zolmitriptan) Nasal Spray.

We acknowledge receipt of your submissions dated the following:

February 27, 2002	August 14, 2002	November 12, 2002
March 6, 2002	September 26, 2002	November 22, 2002
April 15, 2002	October 9, 2002	November 25, 2002
June 27, 2002	November 5, 2002	December 10, 2002
August 12, 2002	November 11, 2002	

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit additional data to demonstrate the bioequivalence of the clinical and commercial (*i.e.*, "to be marketed") spray devices.

As you know, we communicated the deficiency of the *in vitro* testing of the commercial device in a teleconference on 10/9/02 (see enclosure). You submitted a response, in writing, on November 11, 2002. That submission essentially contained two arguments to support bioequivalence of the two devices: one that relies on the existing *in vitro* data, and another based on clinical data from the long-term study 0078. We conclude that your argument relying on the existing *in vitro* data provides no new compelling evidence to support the bioequivalence of the two devices.

We also find the clinical argument problematic. We believe that it is impossible to compare the results contained in part 2 of study 0078 (during which all subjects received the best optimal dose) with those obtained in part 1 (during which subjects were randomized to 0.5mg, 1mg, 2.5mg, or 5mg) because of the potential bias 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 our opinion, favor the commercial device. Furthermore, the results from that study are based on efficacy data across multiple attacks. We 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. We believe that these issues preclude the acceptance of these data as evidence of efficacy of Zomig Nasal Spray when delivered using the commercial device.

In order to address this deficiency, you may consider 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 remind you that  $C_{max}$  and AUC should be bioequivalent. Furthermore, 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 be less efficacious in the treatment of an acute clinical syndrome like migraine, we will also look carefully at  $T_{max}$  as supportive evidence).
3. Provide efficacy data from a well-designed, randomized controlled trial.

In addition, it will be necessary for you to submit revised draft labeling. The attached approvable labeling contains annotations of areas that require further clarification or editing. If additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

Finally, we provide this additional comment, which does not affect the approvability of this application:

The zolmitriptan drug substance specification provided in the current submission incorrectly lists the acceptance criterion for \_\_\_\_\_ as not more than (NMT) \_\_\_\_\_. We remind you that, per your October 21, 1997 submission to NDA 20-768, the limit for \_\_\_\_\_ is NMT \_\_\_\_\_. Please ensure that all applicable documents reflect the correct limit.

When you respond to the above deficiency, include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

Enclosure

25 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ \_\_\_\_\_ § 552(b)(5) Draft Labeling

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/s/

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