CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-239

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-239

COMPLETE RESPONSE

Edward Smith
Sr. Director, Regulatory Affairs
Zogenix, Inc.
5858 Horton Street, Suite 455
Emeryville CA 94608

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated December 28, 2007, received December 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sumavel DosePro (sumatriptan injection).

We acknowledge receipt of your amendments dated the following:

March 20, 2008	July 28, 2008	September 5, 2008
May 2, 2008	July 29, 2008	September 12, 2008
May 19, 2008	August 14, 2008	September 26, 2008
June 16, 2008	August 18, 2008	October 9, 2008
June 18, 2008	August 28, 2008	October 17, 2008
June 18, 2008		

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

NONCLINICAL

1. The positive finding in the in vitro chromosomal aberration assay in human lymphocytes (Study 961611) raises the concern that one or more impurities (e.g., Impurity 1 and Impurity 3) present in the stressed/spiked sumatriptan drug lot tested may have genotoxic potential. Since impurities are unlikely to confer any clinical benefit, the presence of a genotoxic impurity in the clinical drug product, unless unavoidable, is not acceptable. Therefore, you will need to further investigate this issue prior to approval.

   Since we recognize that the conditions used to produce the "stressed" sumatriptan may have resulted in the formation of impurities that would not be formed under normal storage conditions, we would recommend that you conduct a repeat in vitro chromosomal aberration assay in which Impurities 1 and 3 are tested directly. Alternatively, the study

could be conducted using sumatriptan spiked with Impurities 1 and 3 at levels providing a substantial margin above the specification limits. Of course, other approaches may be acceptable. We would recommend that if you choose to test sumatriptan spiked with the impurities, you not use the clinical formulation (12 mg/mL); it artificially limits the concentrations that can be tested.

If this repeat assay is adequately conducted and negative, no further action is necessary. If it is positive, then the genotoxic impurities would need to be identified and specification limits set to a level that would result in a total daily dose of ≤1.5 µg/day of each impurity. If more than one structurally similar impurity is identified, then the specification limits would need to be set so that the combined total daily dose would not exceed 1.5 µg/day. If such limits are not achievable, then additional genetic toxicology studies may be conducted in an attempt to further characterize the genotoxic potential (cf. Guidance for Industry and Review Staff; Recommended Approaches to Integration of Genetic Toxicology Study Results. FDA/CDER, January 2006). If the data from those studies indicated an overall lack of genotoxic potential, then no further action would need to be taken.

2. We acknowledge that you have submitted additional studies (including a 90-day oral toxicity study in rat and an embryo-fetal development study in rabbit) to address the specification limits proposed for Impurities 1 and 3. However, they were not included in the original NDA, and were not submitted in time to allow for review during this cycle. They will need to be reviewed and found adequate prior to approval.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Please submit draft carton and container labeling revised as follows:

Container Label and Carton Labeling

1. Provide better color contrast with the background of the label for the font used to display the proprietary name, established name, and product strength.
2. Increase the prominence of the product strength. Revise the product strength to include the volume in each injection (e.g., 6 mg/0.5 mL).
3. Relocate “DosePro” so it appears immediately following “Sumavel” in order to minimize confusion that the proprietary name is Sumavel DosePro rather than “DosePro Sumavel”.
4. Include the route of administration statement “For Subcutaneous Use Only” on the principle display panel.

Container Label

1. Relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i).

Carton Labeling

1. On the sample 4-pack display carton, relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i) and increase the prominence of the NDC number.
2. Relocate the "See full prescribing information…." statement to the side panel.
3. Include the volume in the net quantity of the carton (e.g., 1 prefilled, 0.5 mL single-dose unit)

TRADENAME

The Division of Medication Error Prevention and Analysis has no objection to the use of the proprietary name Sumavel DosePro for this product provided that a proposed (but not yet approved) proprietary name, associated with a different product, is not approved before this application. In the event that the other product is awarded approval first, we will recommend that you seek an alternative name.

Additionally, if any of the proposed product characteristics are altered prior to approval of your product, we rescind this Risk Assessment finding, and you must resubmit the name for review. Also, if the product approval is delayed beyond 90 days from the date of this letter, your proposed name must be resubmitted for evaluation.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

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

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

16 pages of draft labeling withheld immediately after this page as B4 (TS/CCI)

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

10/31/2008 05:43:03 PM