CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-239

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 14, 2009
From	Eric Bastings, MD.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22239
Applicant	Zogenix
Date of Submission	January 14, 2009
PDUFA Goal Date	July 15, 2009
Proprietary Name / Established (USAN) names	Sumavel DosePro (sumatriptan injection)
Dosage forms / Strength	Injection (subcutaneous needle-free)
Proposed Indication(s)	1. Acute treatment of migraine 2. Cluster headache
Recommended:	*Approval*

1. Introduction

Zogenix is submitting a complete response for their 505(b)(2) application for a needleless sumatriptan autoinjector indicated for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

I refer the reader to my first CDTL memo concerning the development program and basis of approval for this product, which uses as a reference NDA 20-080 for IMITREX injection (6 mg/ 0.5 mL).

2. Background

In the first cycle, the sponsor was issued a complete response letter.

A positive finding in the in vitro chromosomal aberration assay in human lymphocytes raised a concern that impurities present in the stressed/spiked sumatriptan drug lot tested (Impurity 1 and Impurity 3) may have genotoxic potential. The sponsor was requested to further investigate this issue prior to approval. The division recognized 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, and recommended that the sponsor repeat the in vitro chromosomal aberration assay in which Impurities 1 and 3 are tested directly. Alternatively, the division suggested that study could be conducted using sumatriptan spiked with Impurities 1 and 3 at levels providing a substantial margin above the specification limits, and also remained open to other approaches.

The division stated that if this repeat assay was adequately conducted and negative, no further action is necessary. If it is was 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 need to be conducted.

The division also acknowledged that the sponsor had 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, but that as they were not included in the original NDA, and were not submitted in time to allow for review during this cycle, these would need to be reviewed and found adequate prior to approval in the second cycle.

3. CMC/Device

Dr. David Claffey, from ONDQA, reviewed the CMC data. Dr. Claffey recommends approval. There were no CMC approvability issues in the first cycle. Dr. Claffey noted that a "withhold" recommendation from the Office of Compliance (OC) was reversed to "acceptable" on July 13, 2009, upon resolution of the issues identified by OC.

4. Nonclinical Pharmacology/Toxicology

Dr. Charles Thompson reviewed the Nonclinical Pharmacology/Toxicology data. Dr. Thompson concludes that the sponsor has adequately qualified the proposed drug product specification limits (b) (4) for impurity 1 and impurity 3, respectively) in a 90-day subcutaneous toxicity study in rat and a subcutaneous embryo-fetal development study in rabbit, and is recommending approval. Dr. Lois Freed (Dr. Thompson's supervisor) concurs, and also notes that the repeat in vitro chromosomal aberration assay in human peripheral lymphocytes does not suggest a genotoxic concern for either impurity. Dr. Thompson and Freed are recommending approval.

5. Clinical Pharmacology/Biopharmaceutics

There is no outstanding Clinical Pharmacology/Biopharmaceutics issue from the 1st cycle.

6. Clinical/Statistical- Efficacy

There is no outstanding Clinical issue from the 1st cycle.

7. Safety

There is no outstanding Safety issue from the 1st cycle.

8. Advisory Committee Meeting

No advisory meeting was needed for this 505(b)(2) application, because this product is bioequivalent to an already approved marketed product, the Imitrex STATdose System, for which there is sufficient safety experience.

9. Pediatrics

PREA was not triggered for this application.

10. Other Relevant Regulatory Issues

None. The referenced product's patent expired on February 6, 2009.

The Maternal Health Team provided labeling recommendations, which were taken into account, and also recommended that the sponsor establishes a pregnancy registry, to collect additional fetal outcome data and ensure that pregnancy data is collected on all sumatriptan products. I discussed with the Maternal Health Team that the goal of collecting pregnancy data on all sumatriptan products would not be achieved with this pregnancy registry, as there are a number of sumatriptan generics on market (the Imitrex patent expired earlier this year), which were not required to have a pregnancy registry. My expectation is that this new product will only represent a limited portion of the marketplace, given its route of administration (most of the use is for oral products), and will add little to the existing voluntary registry in place for Imitrex. Therefore, the division is not requesting a pregnancy registry as a condition for approval.

11. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) accepted the proposed proprietary name, Sumavel DosePro. DMEPA (Ms. Felicia Duffy) also reviewed the carton and container, and successfully negotiated some changes with the sponsor.

DRISK (Ms. LaShawn Griffiths) reviewed the proposed patient information, and successfully negotiated some changes with the sponsor.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: I recommend approval, as all outstanding issues have been resolved.

Risk Benefit Assessment: This product is bioequivalent to an already approved and marketed product, Imitrex STATdose. This product has a higher rate of local injection site reactions than

Imitrex STATdose, but has the theoretical benefit of a potential to be used by patients with needle phobia.

Recommendation for Postmarketing Risk Management Activities: none.

Recommendation for other Postmarketing Study Commitments: none.

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/s/

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MEDICAL OFFICER