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RESEARCH**

APPLICATION NUMBER:

208223Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 27, 2016
From	Heather Fitter, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208223
Supplement#	
Applicant	Dr. Reddy's Lab
Date of Submission	
PDUFA Goal Date	January 30, 2016
Proprietary Name / Established (USAN) names	Zembrace SymTouch (Sumatriptan Injection)
Dosage forms / Strength	3 mg/0.5 mL subcutaneous injection
Proposed Indication	Acute treatment of migraine with or without aura in adults
Recommended:	Approval

Cross Discipline Team Leader Review

1. Introduction

The applicant, Dr. Reddy's Lab, submitted a 505(b)(2) application for a drug (sumatriptan)/device combination product for the acute treatment of migraine headache with and without aura.

This product is a pre-filled, ready to use, single dose, disposable auto-injector designed to deliver 0.5 mL (3 mg of sumatriptan succinate) into the subcutaneous tissue. The applicant is using as a reference NDA 20080 for Imitrex injection (6mg/0.5 mL) to support the safety and efficacy of their device. The reference listed product (RLD) describes efficacy of this product from 1-6 mg for the acute treatment of migraine with and without aura. The RLD is currently available to be administered at doses of 1-6 mg in an adjustable fashion and as 4 and 6 mg to be administered with an auto-injector. This applicant developed this product as a 3 mg sumatriptan product that can be administered subcutaneously with the use of an auto-injector. The applicant submitted clinical pharmacology studies to support the bioequivalence of their product to a 3 mg dose of Imitrex injection. In addition, a usability study in migraine patients during an attack was submitted as part of this application. The applicant had previously been informed that clinical efficacy trials or long term safety trials would not be required if this product was determined to be bioequivalent to the RLD.

2. Background

Imitrex (sumatriptan) is approved under several formulations for the treatment of migraine: Imitrex injection (NDA 20080), Imitrex tablets (NDA 20132), Imitrex Nasal Spray (NDA 20626) and Sumavel DosePro (NDA 22239)

Two milestone meetings were held that provided direction for this drug development program, a pre-IND meeting (September 30, 2013) and a pre-NDA meeting (March 25, 2015). During the pre-IND meeting FDA agreed that positive results from a well-designed bioequivalence study and positive results from a usability study would potentially support a 505(b)(2) application. During this meeting several issues were discussed that impacted decisions related to labeling.

The applicant stated that one objective of the Zembrace SymTouch development program was to provide a lower effective dose of a sumatriptan auto-injector than what is currently available. Another objective was to (b) (4)

(b) (4) The applicant did not request including this information in the current submission.

On February 25, 2015 a pre-NDA meeting was held; the focus of this meeting was to discuss CMC/Device related issues.

3. CMC/Device

The final recommendation from the CMC review team is to approve Zembrace SymTouch.

CMC Review

Dr. Sherita McIamore Hines was the Drug Substance Quality and Drug product reviewer for this application. Please refer to her review for a full discussion of the issues related to the drug substance review for this application. In summary, the applicant referenced (b) (4) for the manufacture and control, and characterization of the drug substance. Adequate information was submitted to support the characterization and control of potential impurities in the drug substance. The specifications are adequate to ensure the identity, strength, purity and quality of the drug substance, but the applicant did not indicate what tests were used to accept incoming batches of the drug substance, so an IR was sent to the applicant. The applicant responded and provided well described and validated analytic methods for acceptance of drug batches. Adequate container closure and stability information was provided. Based on the review of this information, Dr. Hines concluded that the information provided in the current submission was adequate to support approval.

Drug Product

Zembrace SymTouch injection is a 3 mg/0.5 mL formulation of sumatriptan in a pre-filled syringe fitted into an auto injector. The primary packaging for the drug product is a pre-filled 1 mL clear USP Type I glass syringe fitted with a (b) (4) closure. The

secondary packaging for Zembrace SymTouch injection is the auto injector comprised of a cap (b) (4)

Dr. Hines states in her review that the post-approval stability commitment does not include a plan to test product under accelerated conditions; therefore, the Division sent a comment to the applicant to "update the post-approval stability commitment to include testing under accelerated conditions". The applicant responded with the requested information. In addition, an information request (IR) was sent regarding the analytical method for (b) (4). The method provided was not appropriately validated, so Dr. Hines mentions in her review that the method may not be capable of accurately (b) (4) (b) (4)

(b) (4) A teleconference was held between the applicant and the Agency CMC group on January 7, 2016 to discuss issues related to this impurity. The Agency also communicated to the applicant that calculations of impurities should comply with Imitrex labeling of a maximum daily dose of 12 mg rather than (b) (4) mg as proposed by the applicant. The applicant commits to identify (b) (4)

(b) (4) The applicant plans to accept a shorter shelf life (12 months) than what was requested in the NDA (b) (4)

(b) (4) Following this discussion, CMC notes that they now find the application acceptable for approval.

Product Quality Microbiology Review

Dr. David Bateman was the microbiology reviewer and he also reviewed the syringe process for this product. Dr. Bateman recommends approval of the current NDA based on his review of the application.

CDRH

Dr. Sapana Patel was the reviewer of the prefilled auto-injector for this application. The auto-injector is a fixed single dose disposable (b) (4)

When the injection begins, the user can hear an audible click. The user will hear a second audible click upon completion of the injection. A red plunger rod will be visible through the body window as a signal to the patient that the injection is complete.

Dr. Patel states that his review of the device constituent included the review of the performance of the combination product, biocompatibility of non-drug contacting materials, and the clinical evaluation of the to-be-marketed product to the studied product. The applicant had provided stability studies and provided full test reports for device performance and verification studies. The applicant stated dose accuracy test method captured the audible and visual feedback attributes of the auto-injector. Successful administration of the drug is dependent on the audible feedback mechanism.

The applicant stated that submitted stability studies of the combination product were made using a device prior to two modifications (dimension changes). As part of the design change assessment, the design verification testing was repeated to confirm that the design output met the design input requirements and there were no changes to the

device performance. The to-be-marketed device design that included the modifications was also used in the Summative Human Factors Validation Study.

Required biocompatibility testing was completed and there were no negative biocompatibility findings. However, clinical evaluation of the device identified the device studied as part of the clinical trials was not identical to the to-be-marketed product. Two minor modifications as stated were made to the device and the applicant has indicated that on-going stability testing will include an additional batch with the dimensional changes. The applicant has committed to comply with post approval requirements for testing of the combination product [REDACTED] (b) (4)

Dr. Patel has performed a design review of the submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, Dr. Patel has determined that the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture and after exposure to storage, shipping, and in-use conditions. On 11/30/2015, the applicant provided a post market commitment to the NDA with updated stability results and reported that [REDACTED] (b) (4) will update [REDACTED] (b) (4) as stability data becomes available.

4. Nonclinical Pharmacology/Toxicology

Dr. Charles Thompson conducted the non-clinical review for this application and notes that the current NDA contains no non-clinical data. Dr. Thompson notes in his review that Dr. Hines has not identified any drug product quality issue that raised safety concerns requiring additional non-clinical assessments.

5. Clinical Pharmacology/Biopharmaceutics

The Biopharmaceutics reviewer for this application was Dr. Om Anand. The applicant submitted three clinical pharmacology studies that were conducted to support the pharmacokinetic bridge between Zembrace SymTouch injection and Imitrex injection for this application. The first trial DFP-11/CD/001 failed to meet the required bioequivalence (BE) criteria. Although a root cause analysis was done, the reason for failure was not identified but was determined to not be due to device functionality. The applicant noted that the failure may have been due to consistency/variability of technique of skin pinch and the angle of manual injection and the variability in the amount of injection volume between subjects who received the vial drawn product. The applicant then repeated the BE study with controls in place to eliminate some of the potential causes of failure in the first study, specifically, they modified

the technique of skin pinch and the angle of the manual injection. In addition, they more closely monitored the volume of injection and the residual volumes.

Following the first failed BE study, Study DFP-11/CD/002 was conducted and is considered the pivotal BE study for this application. This study was an open label, single dose, three way crossover study in 36 healthy volunteers (HV) to determine bioavailability of 3 mg Zembrace SymTouch (0.5 mL) vs 3 mg Imitrex (0.25 mL) vs 6 mg Imitrex (0.5 mL). Dr. Anand determined that this study met BE criteria at the 3 mg level as well as dose normalized 6 mg to 3 mg. An additional study (DFP-11/CD/003) was conducted, which was an open label, randomized, single dose, three way crossover study to determine dose normalized BE of Zembrace SymTouch as a 3 mg/0.5 mL injection versus Imitrex STATdose system at 4 mg/0.5 mL and 6 mg/0.5 mL following subcutaneous injection in 36 healthy subjects. Dr. Anand concluded that dose normalized exposure following 3 mg/0.5 mL Zembrace SymTouch injection was BE to that following 4 mg/0.5 mL and 6 mg/0.5 mL Imitrex STATdose injections.

Dr. Om Anand concludes that the overall BE results from these trials support BE of Zembrace SymTouch injection and Imitrex injection and he recommends approval of the current NDA for Zembrace SymTouch injection, 3mg/0.5 mL

Dr. Xiaohan Cai and Dr. Hasan Irier conducted an audit of study DFP-11/CD/002 (the pivotal bioequivalence trial) and concluded that the data from the audited study are reliable.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant is using as a reference NDA 20080 for Imitrex injection (6mg/0.5 mL) to support the safety and efficacy of their product. The division had previously determined that Imitrex injection was effective in the 1-6 mg single dose range for the treatment of migraine with and without aura at the time of review of the RLD, Imitrex (NDA 20080).

8. Safety

Dr. Ramesh Raman reviewed the clinical safety data from the clinical pharmacology studies and noted that there were no reports of death or serious adverse events (SAEs) in any of the studies. He notes that the overall safety profiles including adverse events, injection site reactions, device malfunction or failures of Zembrace SymTouch injection were comparable to that of the referenced drug (Imitrex Injection).

Ms. Justine Harris reviewed the Human Factors (HF) validation study and concluded that the intended users are able to use the proposed product safely and effectively. The HF validation study evaluated migraine patients in three groups of 15 participants each as follows: 1) trained to the use of injection but with no injection experience (trained naïve), 2) untrained naïve and 3) participants that had used injections before but were untrained to this particular device (untrained experienced). All patients were assessed following one unaided injection into either the thigh or upper arm. Ms. Harris concluded that the HF validation study was acceptable and she did not recommend further Human Factors testing. Based on the results of the HF study and Ms. Harris' assessment, I agree that the usability of this product is acceptable.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The Pediatric Research Equity Act (PREA) did not apply to the current application.

11. Other Relevant Regulatory Issues

Not applicable

12. Labeling

The applicant originally proposed the propriety name Zembrace (b) (4) which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was deemed acceptable. The applicant withdrew their request for the name Zembrace (b) (4) and then requested the proprietary name Zembrace SymTouch which was also approved by DMEPA.

DMEPA reviewed the carton and container labels, insert labeling and post marketing data for sumatriptan and identified areas of improvement that were communicated with the applicant and were incorporated into the label. None of the requested revisions were substantive or involved major changes in the IFU; therefore, no additional HF validation study is required.

The applicant initially submitted a label requesting the indication of migraine with and without aura (b) (4) for their product. (b) (4)

Following some additional negotiations that involved several minor items, the applicant indicated their agreement with the Agency on proposed final labeling via an email communication on January 27, 2016 and is in the process of formally submitting the agreed upon label to the NDA.

In addition, the Division of Medical Error Prevention and Analysis (DMEPA) and the Division of Medical Policy Programs (DMPP) reviewed the applicant's proposed instructions for use (IFU), patient package insert (PPI) and carton and container labeling and found them to be acceptable. The Office of Prescription Drug Promotion (OPDP) reviewed the applicant's proposed prescribing information (PI), patient package insert (PPI), instructions for use (IFU), and carton and device labeling and also found them to be acceptable.

13. Recommendations/Risk Benefit Assessment

I recommend approval based on the finding that the currently proposed Zembrace SymTouch 3 mg/0.5 mL injection is bioequivalent to the referenced Imitrex (sumatriptan) injection which the Division has previously determined to be safe and effective for the treatment of migraine with and without aura in adults.

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/s/

HEATHER D FITTER
01/27/2016