CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210884Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	January 25, 2019
From	Heather Fitter, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	210884
Applicant	Dr. Reddy's Laboratories
Date of Submission	March 27, 2018
PDUFA Goal Date	January 27, 2019
Proprietary Name / Established (USAN) names	Tosymra / Sumatriptan nasal spray
Dosage forms / Strength	Nasal spray / 10 mg
Proposed Indication	Acute treatment of migraine with or without aura in adults
Recommended:	Approval

1. Introduction

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

The drug product, DFN-02, is composed of sumatriptan and a (b) (4) called dodecylmaltoside (DDM). The applicant is using Imitrex injection as the listed drug (NDA 20080) to support the safety and efficacy of their product. The label of the listed drug (LD) describes efficacy of this product from 1-6 mg for the acute treatment of migraine with and without aura. The LD is currently available to be administered at doses of 1-6 mg in an adjustable fashion and as 4- and 6-mg doses to be administered with an auto-injector. The maximum dose recommended for administration in a 24-hour period is 12 mg, and doses should be separated by at least one hour.

Imitrex is also marketed as oral tablets in 25-mg, 50-mg, and 100-mg strengths, as well as a nasal spray, with strengths of 5 mg, 10 mg and 20 mg.

The applicant submitted clinical pharmacology studies to establish a pharmacokinetic bridge to the listed drug. The applicant had previously been informed that a long-term local toxicity safety study would be required for approval, and the applicant submitted this study with the current application. The applicant also conducted and submitted the results of a Phase 2 efficacy study with this application, although this study is not required if an acceptable bridge to a listed drug was established.

2. Background

Sumatriptan is approved under several dosage forms for the acute treatment of migraine: Imitrex injection (NDA 20080), Imitrex tablets (NDA 20132), Imitrex Nasal Spray (NDA

20626), Sumavel DosePro (NDA 22239), Zembrace DuoCliq (NDA 208223), and Onzetra (NDA 206099).

Three milestone meetings were held for this drug development program. During the pre-IND meeting in April 2010, the Division agreed that establishing bioequivalence of DFN-02 to Imitrex 6 mg SC could form the basis of a 505 (b)(2) application. At the End of Phase 2 (EOP2) meeting in November 2013, the Division informed the applicant that safety data on a minimum of 100 patients who treated an average of at least 2 migraines per month, for a minimum of 6 months, must be provided with the application. At the pre-NDA meeting in December 2017, the applicant was informed that the pharmacokinetic (PK) profile of their product appears to support the acute migraine indication but not the cluster migraine indication of Imitrex Injection, because the PK profile appeared, on face, to support bioavailability similar to the 4-mg SC dose of Imitrex, but not to the 6-mg dose.

3. CMC/Device

The final recommendation from the Office of Pharmaceutical Quality (OPQ) review team is to approve the application. They conclude, from a quality perspective, that the application provides adequate information to ensure that the applicant can consistently manufacture this product and that it is suitable for use by the intended patients.

Drug Substance

Dr. Raymond Frankewich was the Drug Substance Quality reviewer for this application, and Dr. Suong Tran was the team leader. Please refer to his review for a full discussion of the issues related to the drug substance review for this application. In summary, the applicant referenced DMF (b) (4) for the manufacture and control, and characterization of the drug substance. The information submitted directly to the NDA regarding general properties of sumatriptan, potential impurities, specifications, and analytical procedures, is consistent with the manufacturer's DMF and USP monograph requirements.

Adequate container closure and stability information was provided. Based on the review of this information, Dr. Frankewich and Tran conclude that the information provided in the current submission was adequate to support approval.

Drug Product

Dr. Stephanie Emory was the Drug Product Quality reviewer and Dr. Wendy Wilson-Lee was the team leader. Dr. Emory states that the drug product is a unit-dose nasal spray system that delivers 10 mg sumatriptan in 100 µL of a buffered aqueous solution containing (b) (4) dodecylmaltoside (DDM) (b) (4) In addition to DDM, the formulation contains citric acid monohydrate, potassium phosphate monobasic, sodium phosphate dibasic and sodium chloride. The solution is contained in a (b) (4) single-use nasal spray device. The remaining components of the device are not in product contact until the device is actuated.

Except for DDM, all excipients in the formulation are commonly used in approved nasal products and meet compendial standards. DDM [redacted] has not previously been used in any FDA-approved drug. DDM was developed by [redacted] and supporting CMC information for the excipient is cross-referenced to [redacted] DMF [redacted] The DMF was reviewed in support of the NDA and there are some outstanding deficiencies. However, the DMF is deemed acceptable to support the NDA, as amended, following discussions between the applicant and the DMF Holder. [redacted]

The device component of the product is a [redacted] from [redacted] The general functionality and core design of the device are similar to that of Imitrex and other approved products, e.g., Zomig (NDA 21450) and Narcan (NDA 208411).

The manufacturing process for sumatriptan 10 mg nasal spray involves [redacted] All manufacturing steps are supported by the information provided in the application. [redacted] the product is not required, or intended, to be sterile.

The specification for the finished product includes appropriate physicochemical and device performance tests. Testing includes appearance, assay (for sumatriptan and DDM), pH, osmolality, particulate matter, spray content uniformity (for sumatriptan and DDM), droplet size distribution and spray pattern.

Extractables and leachables were evaluated adequately for the primary container closure and device fluid path components. Three non-mutagenic leachables were detected in the registration batches at long-term conditions, at levels below the threshold of concern.

Primary stability data up to 36 months at long-term conditions demonstrate that the product is sufficiently stable; therefore, the proposed 36-month shelf-life is justified. Additional stability studies demonstrate that the product is stable in simulated shipping conditions and that the device provides adequate light protection to the drug product [redacted] since sumatriptan is photosensitive. Drs. Emory and Wilson-Lee recommend approval of the application.

<u>Product Quality Microbiology Review</u>
Dr. Laura Wasil was the microbiology reviewer and Dr. Ericka Pfeiler was the team leader. The drug product is nonsterile. [redacted]

(b) (4)

(b) (4) The applicant has met regulatory expectations to support the drug product's microbiological quality throughout its shelf life. Drs. Wasil and Pfeiler recommend approval of the current NDA.

CDRH

Dr. Marc Neubauer was the primary reviewer and Dr. Sarah Mollo was the team leader for the review of the nasal spray device for this application. DFN-02 is a clear pale yellow to yellow colored liquid containing sumatriptan (10 mg/0.1 mL). (b) (4)

(b) (4)

(b) (4) he assembled device is further packaged in a single blister with a peel off lid.

The container closure-spray device is a unit dose combination (drug/device) product. The device contains (b) (4) of a 100 mg/mL aqueous buffered solution of sumatriptan, and is designed to deliver a single spray of 100 uL containing 10 mg of sumatriptan. DFN-02 is a disposable single dose product and priming is not required prior to administration. The general functionality and core design of the DFN-02 nasal spray device are similar to the approved products such as Imitrex (NDA 020626), Zomig (NDA 021450) and Narcan (NDA 208411).

Dr. Marc Neubauer states that this review includes a review of the essential performance requirements, design verification, design validation, stability, shipping validation, risk analysis and finished product specification. This review does not involve biocompatibility or human factors. Dr. Neubauer concludes that the device constituents parts of the combination product are approvable.

Dr. Neubauer concludes that the essential performance requirements are acceptable. Specifically, the data provided by the applicant for design verification and stability testing of their essential performance criteria all passed their acceptance criteria. Shipping validation was acceptable. In addition, their risk analysis is acceptable.

Dr. Neubauer states that the DFN-02 Unit dose nasal spray device is similar to several marketed products (e.g., Narcan, Imitrex, Zomig) (b) (4)

The applicant conducted a series of evaluations to identify if there are any new or unique risks associated with the use of the proposed DFN-02 product when compared to the similar combination products and Dr. Neubauer concludes, after review of this information,

that DFN-02 does not introduce any new risks into the market place, hence not requiring further human factors validation.

Dr. Neubauer 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. Drs. Neubauer and Mollo conclude that the device constituents parts of the combination product are approvable.

4. Nonclinical Pharmacology/Toxicology

Dr. Edmond Nesti conducted the non-clinical review for this application and Dr. Lois Freed conducted the secondary review. Dr. Nesti notes that the current NDA includes an adequate nonclinical evaluation of DFN-02 and the novel excipient, DDM. Drs. Nesti and Freed conclude that the nonclinical package supports approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology primary reviewer for this application was Dr. Priya Brunsdon; the secondary review was conducted by Dr. Bilal AbuAsal, and the team leader was Dr. Sreedharan Sabarinath. This application relies on the results of a pivotal relative bioavailability study (DFP-02-CD-009), which was a three-way crossover study conducted in 78 healthy subjects with Tosymra 10 mg and the listed drug, Imitrex 4-mg and 6-mg injection.

The applicant conducted 6 pharmacokinetic studies and one pivotal relative bioavailability study in healthy volunteers. Four of the studies explored formulation development, one assessed dose-proportionality and one was a dose-finding study. A placebo-controlled efficacy study and an open-label long-term extension study were conducted for the clinical program and will be discussed in Section 7 and 8 of this memo.

The pivotal relative bioavailability study was a randomized three-way crossover study to compare the pharmacokinetics, safety and tolerability of intranasal Tosymra 10 mg and subcutaneous 6 mg and 4 mg sumatriptan in healthy adult subjects. Doses were administered under fasting condition. The pivotal study used the final to-be-marketed formulation of Tosymra. Bioequivalence between the test treatment and the reference treatment would be concluded if the 90% confidence interval of the ratio (test/reference) of in-transformed C_{max}, AUC $_{0\text{-last}}$, and AUC $_{0\text{-inf}}$ values were within 0.80 to 1.25.

As illustrated in Table 1 and Table 2, Tosymra did not meet the criteria for bioequivalence when compared to the 6-mg Imitrex injection dosage strength, but met bioequivalence criteria with Imitrex injection 4 mg. Tosymra achieved a maximum concentration by approximately 10 minutes after administration, and had an elimination half-life of approximately 2.4 hours.

Table 1: Study DFP-02-CD-009 - Comparison of Plasma Sumatriptan PK Parameters: 10-mg Tosymra vs. 4- mg Imitrex SC Injection (source-Table 1 of Dr. Brunsdon's review)

	Geometric LSM			
Pharmacokinetic Parameters	**10-mg TOSYMRA intranasal spray (test, N = 73)**	**4-mg Imitrex SC injection (N = 75)**	**Geometric Mean Ratio (%)**	**90% Confidence Interval**
C_{max} (ng/mL)	51.75	49.02	105.57	95.97 - 116.13
AUC_{0-t} (ng*hr/mL)	59.71	68.09	87.69	82.14 - 93.61
AUC_{0-inf} (ng*hr/mL)	60.64	69.16	87.68	82.14 - 93.58

Table 2: Study DFP-02-CD-009 - Comparison of Plasma Sumatriptan PK Parameters: 10-mg Tosymra vs. 6-mg Imitrex SC Injection (source- Table 2 of Dr. Brunsdon's review)

	Geometric LSM			
Pharmacokinetic Parameters	**10-mg TOSYMRA intranasal spray (N = 73)**	**6-mg Imitrex SC injection (N = 75)**	**Geometric Mean Ratio (%)**	**90% Confidence Interval**
C_{max} (ng/mL)	51.75	72.78	71.10	64.63 - 78.21
AUC_{0-t} (ng*hr/mL)	59.71	102.78	58.10	54.42 - 62.02
AUC_{0-inf} (ng*hr/mL)	60.64	103.87	58.38	54.71 - 62.29

Dr. Brunsdon concludes that the study showed Tosymra 10-mg intranasal spray met bioequivalence criteria with the 4-mg dose of Imitrex subcutaneous injection, based on C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Tosymra had significantly lower exposure than the 6-mg dose of Imitrex injection. Since the 4-mg Imitrex dose is approved for the indication of acute migraine, but not for cluster headache, Tosymra can only be approved for the indication of acute migraine. First pass metabolism for subcutaneous and nasal sprays are expected to be minimal and thus, metabolic profiles are expected to be similar for Tosymra and the listed drug. Dr. Brunsdon recommends that all labeling pertaining to intrinsic and extrinsic factors should be the same as in the label for the listed drug.

A consult request for clinical and bioanalytical site inspections for the pivotal bioavailability study was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS recommended accepting the data without an on-site inspection.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Laura Jawidzik conducted the clinical review and Dr. Jinnan Liu conducted the statistical review, with Dr. Kun Jin serving as the statistical team leader. The applicant is using as the

listed drug (LD) NDA 20080 for Imitrex injection (6 mg/0.5 mL) to support the systemic safety and efficacy of their product. The Division had previously determined that Imitrex injection is effective in the 1-6 mg single-dose range for the acute treatment of migraine with and without aura (NDA 20080). The applicant therefore may rely on this listed drug to support both the efficacy and safety of their product. Table 3 below describes the studies discussed in this memo, and they will be referred to as Study 012, 010, and 009, respectively, in the text below.

Table 3: Listing of Clinical Trials Relevant to this Application (source: Table 1 of Dr. Jawidzik's review)

Trial Identity	Trial Design	Regimen/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled
DFN-02-CD-012	Randomized, double-blind, placebo-controlled	Single 10-mg nasal dose with option for a second dose	2-hour pain freedom	Single attack/ Within 2 to 7 days post dose	107 randomized; 93 treated; 74 completed
DFN-02-CD-010	Open-label safety study	Single 10-mg nasal dose with option for a second dose	Safety/tolerability	6 months/ Every 30 days for 6 months	173 enrolled; 167 treated; 134 completed
DFP-02-CD-009	Open-label, single-dose, 3-way crossover study	Single 10-mg nasal, 4-mg SC, or 6-mg SC dose	PK parameters	6 weeks	78 enrolled; 77 completed

Although an efficacy study was not required for approval of this application, as an acceptable pharmacokinetic bridge to the listed drug was provided, the applicant conducted an efficacy study and submitted this study to the application, (b) (4) Study 012 was a randomized, double-blind placebo-controlled, efficacy study of 107 patients with migraine, randomized in a 1:1 ratio to placebo or DFN-02. Patients were allowed to treat a single migraine attack with study medication (which will be referred to as DB1). Patients who treated a migraine in DB1 were eligible to be re-randomized for treatment of a second migraine attack (DB2). The primary efficacy endpoint was the proportion of patients who were pain-free at 2 hours (DB1) after the first dose of medication. There was no prespecified plan in place to control for errors of multiplicity; therefore, none of the secondary endpoints was formally evaluated. The statistical analysis plan (SAP) was not sent to the IND in advance of study initiation, and therefore, the Division was not able to review the SAP and provide comments. In fact, the SAP was submitted to the IND at the time of submission of the complete study report. In the SAP, the applicant defined their full analysis set (FAS), which was used for the primary analysis, as all randomized patients who took at least one dose of study medication during DB1 and had at least one post-baseline efficacy timepoint. Patients who took rescue medication prior to the 2-hour timepoint were excluded from the primary analysis by the applicant. In addition, missing data were to be handled using the last observation carried forward (LOCF). The applicant presented an analysis of the primary endpoint demonstrating a (b) (4) improvement for DFN-02 compared to placebo in headache pain-freedom at 2 hours post-dose (Table 4). DFN-02 was not significantly better than placebo for pain-freedom at two hours in the DB2 period.

(b) (4)

Both Dr. Jawidzik, the clinical reviewer, and Dr. Liu, the statistical reviewer, conclude that due to poor data quality and issues with data analysis, Study 012 does not provide evidence of efficacy. The statistical team noted a number of deficiencies in the applicant's analysis of the data, and was not able to replicate the applicant's analysis. (b) (4)

Dr. Liu notes that a substantial number of subjects who were randomized had no valid observed values for the primary efficacy measurement (see Table 5). Dr. Liu also notes that the pre-specified missing data method of LOCF is not an acceptable method of imputation, as documented in the finalized ICH E9(R1) addendum (the SAP was provided at the time of the CSR submission, and not in advance, so FDA was not able to provide comments to the applicant). Dr. Liu also objects to the selection of the primary analysis set, which excludes patients who took rescue medication within 2 hours of study medication administration. These patients must be included in the primary analysis. Table 5 shows an imbalance between treatment groups in the amount of missing data, with approximately twice the amount of missing data in the placebo group as compared to the active treatment group. Dr. Liu also notes that she was unable to verify the applicant's analysis due to data quality issues, even after submitting information requests (IR) to the applicant and reviewing the applicant's responses. She also tried to conduct a sensitivity analysis using observed data only, but was unable to conduct this analysis due to dataset flag inaccuracies; therefore, she was unable to present independent analyses in her review. Dr. Liu states that due to the small sample size in this study, an incorrect treatment success assignment of one patient changes the p-value from a statistically significant to a non-statistically significant level, and review of the data suggests incorrect treatment assignment may have occurred for several patients.

Table 5: Study DFN-02-CD-012-Patient Disposition (source: Table 8 of Dr. Liu's review)

Patient Counts	Placebo	Treatment	Total
Passed Screening and Randomized	53	54	107
With Assessment for Pain Free Status at 2 hours with LOCF	43	50	93
With Non-missing Assessment for Pain Free Status at 2 hours	39	48	87
With Non-missing Assessment for MBS Status at 2 hours	37	41	78

Overall, due to the unacceptable definition of the FAS for the primary outcome, the incorrect treatment outcome assignments in certain cases, an inability to adjudicate the applicant's data regarding treatment outcomes to independently validate the primary analysis, and the unacceptable way of handling missing data for the primary analysis, the applicant's results of this study cannot be considered reliable and (b) (4)

The pivotal bioavailability study demonstrates that DFN-02 met bioequivalence criteria with Imitrex 4 mg SC. Since efficacy has been demonstrated for Imitrex SC 4 mg, this application provides substantial evidence of efficacy for DFN-02 for the treatment of acute migraine with and without aura. Study 012 is not needed to support approval of this product, (b) (4) (b) (4) since it is not of sufficient quality to provide additional support of efficacy of this product.

8. Safety

Dr. Laura Jawidzik reviewed the clinical safety data from the pivotal clinical pharmacology study (009), the Phase 2 study (012), and the long-term safety study (010). The long-term safety study was a 6-month safety study to assess the intranasal local toxicity of chronic use of DFN-02. At the EOP2 meeting, the applicant was asked to provide safety data on at least 100 patients that treated on average at least 2 migraines per month for 6 months. The applicant provided long-term safety data on 97 patients, which was deemed acceptable.

She notes that there were no reports of death or serious adverse events (SAEs) in these three studies. She also notes that the overall systemic safety profile, including adverse events, was comparable to that of the listed drug (Imitrex Injection). The intranasal local toxicity adverse events were notable in this trial and were higher than those recorded in Study 012 (refer to Table 6, Table 7, and Table 8). An evaluation of the local intranasal toxicity findings will be the subject of this section of the memo.

Table 6: Study DFN-02-CD-010: Common Local Adverse Reactions (source: modified from Table 18 of Dr. Jawidzik's review)

	Total (N=167)
Application site reactions*	36 %
Dysgeusia	21 %
Throat irritation	5%
Lacrimation	2%

*PT terms group for this calculation are application site reactions, application site irritation, application site pain, and application site paresthesia

Table 7: Study DFN-02-CD-012(DB1)-Adverse Events Reported at a Greater Frequency than Placebo (source: Table 19 Dr. Jawidzik's review)

	DFN-02 N=50 (%)	Placebo N=43 (%)
Application site reactions	6	0
Dysgeusia	2	0
Chest discomfort	2	0
Diarrhea	2	0
Hyperkalemia	2	0
Laceration	2	0

Table 8: Study DFN-02-CD-010 (DB2): Adverse Events reported at a Greater Frequency than Placebo (source: Table 20 Dr. Jawidzik's review)

	DFN-02 N=37 %	Placebo N=38 %
Dysgeusia	8	0
Sinusitis	5	0
Application site pain	3	0
Rash (Allergic dermatitis)	3	0
Malaise	3	0
Ear infection	3	0
Laceration	3	0

Dr. Jawidzik concludes that the rates of adverse reactions were low in the double-blind treatment period (Study 012) but notes that these patients only treated one or two migraines during the study. She also notes that the placebo group had no intranasal local toxicity adverse events reported, which is somewhat unusual. Dr. Jawidzik recommends describing the local adverse event rate from the open-label long-term safety study (Study 010) in the label. Since the open-label study is more reflective of how the product will be used (e.g., to treat multiple migraine headaches), it seems most appropriate to include this data in the label. In addition, Study 009 shows that the local application site reactions are much higher than would be suggested by study 012. Out of 78 patients studied, 17% reported dysgeusia, 6% experienced headache, nasal discomfort and throat irritation. It is not apparent as to why the number of AEs in Study 012 is so low, as compared to Study 009 and 010.

9. Controlled Substance Staff

Dr. Shalini Bansil was the primary reviewer for the controlled substance review and Dr. Martin Rusinowitz was the team leader. They agree with the applicant's assessment that Tosymra does not require scheduling under the Controlled Substance Act, and that Section 9, Drug Abuse and Dependence, need not be included in the product label.

10. Advisory Committee Meeting

Not applicable

11. Pediatrics

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

12. Other Relevant Regulatory Issues

Not applicable.

13. Labeling

The applicant proposed the propriety name Tosymra which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was deemed acceptable.

In addition, 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.

The applicant indicated their agreement with the Division on proposed final labeling via an email communication on January 25, 2018 and is in the process of formally submitting the agreed upon label to the NDA.

14. Recommendations/Risk Benefit Assessment

I recommend approval of this NDA for Tosymra based on the finding that Tosymra 10 mg nasal spray meets bioequivalence criteria with the 4-mg dose of 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. Systemic safety of this product was comparable to the listed drug. The long-term safety of the product is acceptable. Overall, the risk/benefit assessment is acceptable and similar to that of previously approved sumatriptan products.

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/s/

HEATHER D FITTER
01/25/2019 12:43:56 PM

ERIC P BASTINGS
01/25/2019 01:12:18 PM
I concur.