CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210884Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number:	210884
Link to EDR	\\CDSESUB1\evsprod\NDA210884\0000
Submission Type:	Original NDA (505(b)(2))
Associated IND:	108088
Applicant:	Dr. Reddy's Laboratories, Ltd.
Submission Date:	March 27, 2018
Brand Name:	TOSYMRA®
Generic Name	Sumatriptan
Dosage Form:	Nasal spray
Dosage Strength:	10 mg/0.1 mL
Proposed Indication:	Acute treatment of migraine with or without aura in adults
Proposed Dose:	10 mg given as a single spray in one nostril. The maximum cumulative dose that may be given in a 24-hour period is 30 mg, with doses separated by at least 1 hour.
OCP Division:	DCP1
Primary Reviewer:	Priya Brunsdon, Pharm.D
Secondary Reviewer:	Bilal AbuAsal, Ph.D
Team Leader:	Sreedharan Sabarinath, Ph.D

Contents

1. Executive Summary

Dr. Reddy's Laboratories Ltd. submitted a New Drug Application (NDA) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for a 10 mg sumatriptan nasal spray (TOSYMRA®). This submission relies on the findings of safety and efficacy of IMITREX® (NDA 020080) subcutaneous injection (sumatriptan succinate), approved on 12/28/1992, as the listed drug[1]. For the indication of acute treatment of migraine with and without aura, IMITREX® injection is approved for use as single doses of 1 to 6 mg with a maximum daily dose of 12 mg in a 24 hour period. IMITREX® injection is also approved for the acute treatment of cluster headache in adults at the 6 mg dose only. For the treatment of cluster headache, the efficacy of lower doses has not been established.

This application relies on the results from a pivotal relative bioavailability study (DFP-02-CD-009), a three-way crossover study conducted in healthy subjects with TOSYMRA® (10 mg) and the listed drug (IMITREX® 4 mg and 6 mg injections). This study demonstrated bioequivalence between TOSYMRA® and the 4 mg subcutaneous IMITREX injection based on C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. TOSYMRA® did not achieve bioequivalence to the 6 mg IMITREX dose level.

A consult request for clinical and bioanalytical site inspections for Study CFP-02-CD-009 was sent to the Office of Study Integrity and Surveillance (OSIS) on May 17, 2018. The inspection request was assessed by OSIS and they recommended accepting data without an on-site inspection. See Bioequivalence Establishment Inspection Report Review (6/21/2018) for details.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval of TOSYMRA® for acute treatment of migraine with or without aura in adults. This recommendation is based on the bioequivalence demonstrated for TOSYMRA® to the listed drug IMITREX® 4 mg subcutaneous injection.

OCP does not recommend approval for cluster headache, without additional studies.

2. Background and Regulatory History

Sumatriptan is a 5HT-1B/1D receptor agonist approved for the treatment of acute migraine in adults in 1992. It is metabolized primarily by MAO-A and excreted in the urine as its major metabolite, indole acetic acid (IAA). The elimination half-life of sumatriptan is approximately 2.5 hours and it is excreted primarily in the urine (about 60%) as unchanged sumatriptan (about 22%) and as the IAA metabolite (about 38%). Current approved dosage forms include oral tablets, subcutaneous injections, nasal sprays, inhalation powders, and transdermal patches.

[1] IMITREX™ (sumatriptan succinate) USPI: { https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020080s052lbl.pdf}

Prior to the submission of this NDA on March 27, 2018, the investigational drug was studied under IND 108088. Notable regulatory meetings with the applicant include an End-of-Phase 2 meeting where the agency agreed that the proposed pivotal study design (DFP-02-CD-009) would be adequate to bridge to the listed drug and no further PK studies would be required (See IND 108088 Meeting Minutes dated 12/4/2013). Additionally, a pre-NDA meeting was held, and the applicant was advised by the agency that TOSYMRA® is not sufficiently similar to the 6 mg dose of IMITREX® to support the indication of cluster headache. This is because efficacy for cluster headaches has only been demonstrated at the 6 mg dose level of the listed drug (See IND 108088 Meeting Minutes dated 3/16/2018).

The applicant conducted 6 pharmacokinetic studies and one pivotal relative bioavailability study in healthy volunteers (DFP-02-CD-009). Four studies were aimed at formulation development (1931/09, 2010/10, 1756/09, 1932/09), one assessed dose-proportionality (2419/11), and one was a dose-finding study (DFP-02-CD-08). A summary of the studies that were conducted as part of the clinical development program are listed in **Table 4**. Additionally, a placebo-controlled efficacy study (DFN-02-CD-012) and an open-label long-term safety study (DFP-02-CD-010) was conducted in migraine patients. Please refer to the Clinical Review by Dr. Laura Jawidzik for additional information regarding the open-label safety study.

The pivotal study DFP-02-CD-009 is the only one described in this review as it was adequate to support this application. This study (DFP-02-CD-009) was conducted using the final to-be-marketed formulation of TOSYMRA® and the listed drug (Imitrex® 4 mg and 6 mg) using a three-way cross-over design in healthy adults.

3. Summary of Pivotal Relative Bioavailability Study

Study Title: 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

Methodology:
This was an open-label, randomized, three-way crossover study conducted in healthy adult volunteers under fasting conditions to assess the bioequivalence, safety and tolerability of a single dose of 10 mg TOSYMRA®. All doses were administered by a healthcare professional and subjects remained confined to the clinical research unit until after the 24-hour blood draw.

Blood Sampling for PK: Blood samples were collected pre-dose (0 hours), 0.083, 0.167, 0.25, 0.333, 0.416, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose. The washout period was at least 3 days (~12 half-lives) between each dose of sumatriptan and was sufficient to ensure the elimination of the sumatriptan dose.

Number of Subjects Enrolled and Randomized:
N=78 healthy adults enrolled and randomized. Seventy-seven subjects completed the study after one subject was discontinued for using a forbidden concomitant medication.

Main Criteria for Inclusion:
Healthy adults 18 – 45 years old, with BMI ≥ 18.0 and ≤ 32.0 kg/m^2, who do not use tobacco or nicotine products.

Test and Reference Products:
Treatment A: 10 mg TOSYMRA® nasal spray
Treatment B: IMITREX 6 mg/0.5 mL subcutaneous injection STATdose Pen
Treatment C: IMITREX 4 mg/0.5 mL subcutaneous injection STATdose Pen

Subjects were randomized to 1 of 6 sequences: ABC, BCA, CAB, ACB, BAC, or CBA.

Criteria for BE Assessment:
Bioequivalence between the test treatment and the reference treatment was concluded if the 90% confidence interval of the ratio (test/reference) of ln-transformed C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ values are within 0.80 to 1.25.

Results:
For the comparison of TOSYMRA® with the 4 mg Imitrex® injection, the ratio (test/reference) of the geometric means of C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ were 1.05, 0.88, and 0.88, respectively. The 90% confidence intervals of the LS Mean ratios were within 0.8 to 1.25. The rate and extent of absorption of TOSYMRA® and the 4 mg Imitrex® injection were within the acceptable boundaries for bioequivalence (**Table 2**).

Table 1. Statistical Comparison of Plasma Sumatriptan PK Parameters: 10 mg TOSYMRA® vs 4 mg Imitrex SC Injection

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

(Source: Clinical Study Report DFP-02-CD-009 page 53, In-Text Table 10, Link \\cdsesub1\evsprod\nda210884\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\dfn-02-cd-009\dfn-02-cd-009-report-body.pdf)

The results of TOSYMRA® compared to the 6 mg Imitrex injection showed the ratio (test/reference) of the geometric means of C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ to be 0.71, 0.58, and 0.58, respectively. The 90% confidence intervals of the LS Mean ratios are entirely outside of the 0.8

to 1.25 range. The rate and extent of absorption of TOSYMRA® is significantly less than the 6 mg IMITREX injection and therefore did not meet the criteria for bioequivalence at this dose level (**Table 3**).

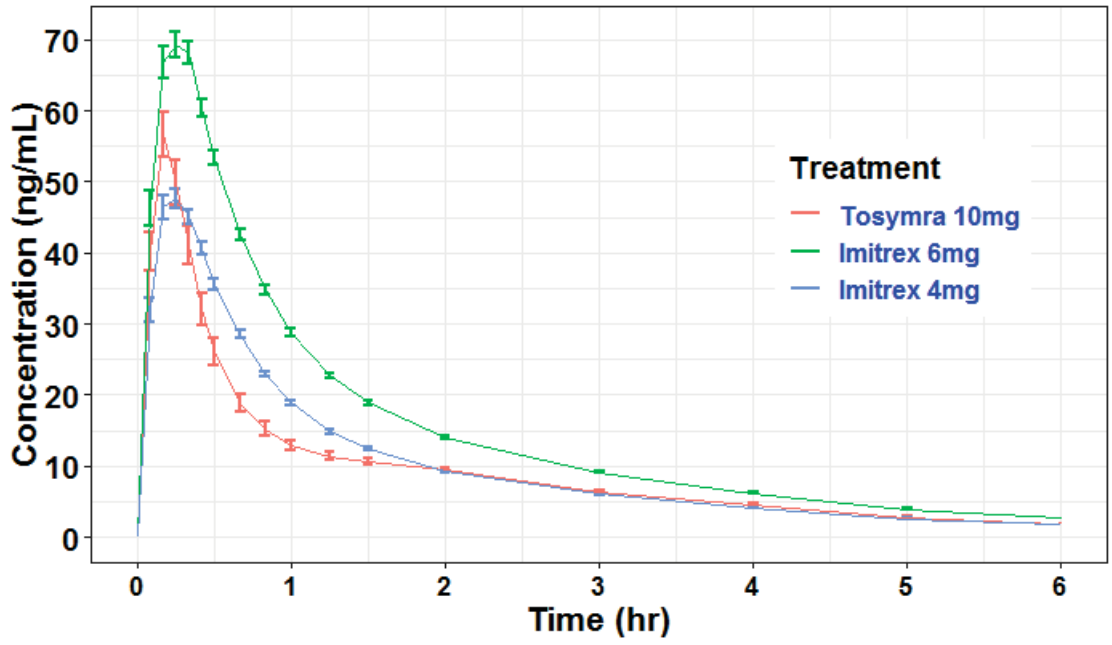
Table 2. Statistical Comparison of Plasma Sumatriptan PK Parameters: 10 mg TOSYMRA® vs 6 mg Imitrex SC Injection

	Geometric LSM			
Pharmacokinetic Parameters	**Treatment A 10 mg TOSYMRA® intranasal spray**	**Treatment B 6 mg Imitrex® SC injection (reference, 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

(Source: Clinical Study Report DFP-02-CD-009 page 51, In-Text Table 8, Link \\cdsesub1\evsprod\nda210884\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\dfn-02-cd-009\dfn-02-cd-009-report-body.pdf)

The pharmacokinetic profiles resulting from a single dose administration of 10 mg TOSYMRA®, 4 mg and 6 mg IMITREX® injections are shown in **Figure 1**.

Figure 1. Mean (±SE) Sumatriptan Plasma Concentration for Tosymra 10mg, Imitrex 4mg, Imitrex 6mg (N = 78) – Study DFP-02-CD-009



(Source: DFP-02-CD-009 Data Analysis Dataset, ADPC, Link \\cdsesub1\evsprod\nda210884\0000\m5\datasets\dfn-02-cd-009\analysis\adam\datasets\adpc.xpt)

TOSYMRA® achieved a maximum concentration by about 10 minutes and had an elimination half-life of approximately 2.4 hours.

It should be noted that one subject (Subject 22) was a statistical outlier that was excluded from the final analyses. After administration with TOSYMRA® nasal spray, the resulting PK parameters for Subject 22 ($AUC_{0\text{-}inf}$ = 5.72 ng-hr/mL, C_{max} = 2.43 ng/mL) was significantly lower than the population mean exposure ($AUC_{0\text{-}inf}$ = 64.74 ng-hr/mL, C_{max} = 58.08 ng/mL). There was no documentation regarding sneezing, nasal discharge, or device malfunctioning that could have caused the low exposure. The studentized residuals for Subject 22 were -7.17, -7.59, and -7.52 for ln (C_{max}), ln ($AUC_{0\text{-}t}$), and $AUC_{0\text{-}inf}$, respectively. The agency agreed to treat Subject 22 as a statistical outlier in a communication on April 2, 2015 (See Meeting Minutes for IND 108088 on 4/02/15).

Conclusion:

The study demonstrated bioequivalence with the 4 mg subcutaneous IMITREX injection based on C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$. TOSYMRA® had significantly lower exposure than the 6 mg IMITREX dose and did not achieve bioequivalence to that dose level. Since the 4mg Imitrex dose is approved for the indication of acute migraine, but not for cluster headaches, 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 as a result, metabolic profiles are expected to be similar for TOSYMRA® and the listed drug. All labeling pertaining to intrinsic and extrinsic factors will be same as in the label for the listed drug (Imitrex® subcutaneous injection).

4. Bioanalytical Method Validation

For the determination of sumatriptan concentrations in human EDTA K3 plasma over the range of 100 to 150000 pg/mL, the Applicant used a validated High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry detection (HPLC-MS). This method was developed and validated by (b) (4) The method for the determination of sumatriptan in human plasma was in compliance with the standards established by the FDA Bioanalytical Method Validation Guidance (2018) and was shown to be precise, accurate, sensitive and selective over the validated range. The validation parameters are summarized in **Table 3**.

Table 3. Bioanalytical Method Validation Summary

Parameter	Value
Analyte	Sumatriptan
Internal standard (IS)	Sumatriptan-d_6
Limit of quantitation (pg/mL)	100 to 150000 pg/mL
Average recovery of drug (%)	64.37 – 68.86
Average recovery of IS (%)	66.55
Standard curve concentrations (ng/mL)	10, 20, 300, 750, 1500, 2000, 6000, 12000, 15000
QC concentrations (ng/mL)	LLQC: 10, QC1: 30, QC2: 7500, QC3: 11250
QC Intraday precision range (%)	0.7 – 7.28
QC Intraday accuracy range (%)	-7.95 – 12.38
QC Inter-day precision range (%)	2.92 to 18.84 *The precision at the LLOQ (100 pg/mL) was 18.84%. This meets the acceptance criteria of +/-20% at the LLOQ. All other concentrations above 100 pg/mL had precision <15% in accordance with the FDA Bioanalytical Method Validation Guidance.
QC Inter-day accuracy range (%)	-9.02 to 11.35
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	23h 43min at room temperature
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Sumatriptan: 588 days at -20°C Internal Standard: 50 days at -20°C
Processed stability (hrs) (equivalent to post-preparative stability)	71h 06min at room temperature
Freeze-thaw stability (cycles)	4 cycles at -20ºC
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	63 days at -20°C

5. Appendix

Table 4. Summary of Completed Clinical Studies

Study No.	Study Description
1931/09	Phase 1 blinded, randomized, balanced, 3-treatment, 3-period, 3-sequence, single dose crossover study of the PK, safety, and tolerability of 3 formulations of sumatriptan nasal spray (N = 18)
2010/10	Phase 1 blinded, randomized, balanced, 4-treatment, 4-period, 4-sequence, single-dose crossover study of the PK, safety, and tolerability of 3 formulations of sumatriptan nasal spray (N = 24)
2419/11	Phase 1 open-label, randomized, balanced 3-treatment, 3- period, 3-sequence, single-dose crossover study of the PK, safety, and tolerability of 3 DFN-02 doses (N = 18)
DFP-02-CD-008	Phase 1 randomized, placebo-controlled, single-dose, 4-way crossover study of the PK, safety, and tolerability of 2 doses of DFP-02 versus subcutaneous 6 mg Imitrex and the PK of DDM (N = 16)
1756/09	Early development randomized, balanced, open label, 3-treatment, 3-period, 3-sequence crossover study of the bioavailability and safety of 2 formulations of sumatriptan nasal spray, 20 mg relative to Imitrex nasal spray (N = 18)
1932/09	Early development blinded, randomized, balanced, 4-treatment, 4-period, 4-sequence, single dose crossover study of the PK and safety of 3 formulations of sumatriptan nasal spray, 20 mg relative to Imitrex nasal spray (N = 24)
DFP-02-CD-009	Phase 1 open-label, randomized, single-dose, 3-way crossover study under fasting conditions evaluating PK, safety, and tolerability of DFP-02 versus subcutaneous 6 mg and 4 mg Imitrex and the PK of DDM (N = 78)
DFP-02-CD-010	Phase 3 multi-center, open-label, all active doses study of the long-term safety of DFN-02 (N = 167)
DFN-02-CD-012	Phase 2 multi-center, double-blind, parallel arms, placebo-controlled study of the efficacy and safety of DFN-02 (N = 93)

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/s/

PRIYA BRUNSDON
12/14/2018

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12/14/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/21/2018

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210884

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Hill Top Research, Inc.	1930 Heck Avenue, Building 2, Neptune City, NJ
Analytical	(b) (4)	(b) (4)

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/s/

SHILA S NKAH
06/21/2018