

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210884Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 210884
Review 1**

Drug Name/Dosage Form	Tosymra™ (sumatriptan) nasal spray
Strength	10 mg
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	N/A

Quality Review Team

Discipline	Primary Reviewer	Secondary Reviewer
Drug Substance	Ray Frankewich	Su Tran
Product and Labeling	Stephanie Emory	Wendy Wilson-Lee
Process	Tianhong Tim Zhou	Nallaperumal Chidambaram
Microbiology	Laura Wasil	Erica Pfeiler
Facility	Tianhong Tim Zhou	Ying Zhang
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

Submissions Reviewed	Document Date	Disciplines Affected
SD-1, Original submission	03/27/2018	All
SD-4, Response to IR	05/23/2018	Product, Process
SD-6, Response to IR	06/15/2018	Microbiology
SD-7, Response to IR	06/28/2018	Device (CDRH)
SD-9, Response to IR	07/19/2018	Process
SD-11, Response to IR	08/06/2018	Device (CDRH)
SD-13, Labeling/Container	08/31/2018	Labeling
SD-14, Response to IR	09/07/2018	Product, Process
SD-17, Labeling/Container	10/09/2018	Labeling
SD-18, Response to IR	11/02/2018	Device (CDRH)
SD-19, Response to IR	11/02/2018	Drug substance, Facility
SD-20, Response to IR	11/19/2018	Drug substance
SD-22, Response to IR	11/26/2018	Product
SD-24, Response to IR	12/07/2018	Product
SD-25, Response to IR	12/10/2018	Product
SD-28, Response to IR	12/20/2018	Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate ¹	--	
(b) (4)	IV	(b) (4)		Adequate for NDA 210884 ²	12/20/2018	Reviewed by S. Emory
(b) (4)	III	(b) (4)		N/A ³	--	
(b) (4)	III	(b) (4)		N/A ³	--	
(b) (4)	III	(b) (4)		N/A ³	--	
(b) (4)	III	(b) (4)		N/A ³	--	
(b) (4)	III	(b) (4)		N/A ³	--	

¹ Based on review by DLAPI dated 09/26/2018

² Adequacy of the DMF is based on commitments made by DRL under the NDA.

³ Adequate information was provided in the NDA. Thus, the DMFs were not reviewed.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
NDA	20080	GSK NDA for Imitrex injection
NDA	20626	GSK NDA for Imitrex nasal spray Strengths: 5 mg, 10 mg (discontinued), and 20 mg
IND	108088	DRL IND for development of DFN-02 (sumatriptan nasal spray 10 mg)

2. CONSULTS

Device aspects were consulted to CDRH and reviewed by Marc Neubauer. His consult review memorandum recommends approval of the NDA.

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends **Approval** of NDA 210884, Tosymra™ (sumatriptan) nasal spray. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) Including Intended Patient Population	Acute treatment of migraine in adults
Duration of Treatment	Chronic - intermittent
Maximum Daily Dose	30 mg
Alternative Methods of Administration	None

Sumatriptan is a selective 5-HT_{1B/1D} receptor agonist that was initially approved in 1992 for treatment of migraine and cluster headaches under the tradename Imitrex®. The innovator, GlaxoSmithKline (GSK) initially marketed Imitrex as tablets and an injectable formulation containing sumatriptan succinate. Subsequently, GSK developed a nasal spray formulation containing sumatriptan as the free base. Generic equivalents of the Imitrex products are available and additional dosage forms developed by other firms have been approved under 505(b)(2) applications.

Dr. Reddy's Laboratories (DRL) seeks approval of a novel sumatriptan nasal spray product. The principal difference between DRL's product and Imitrex nasal spray is inclusion of a novel (b) (4) dodecylmaltoside¹ (DDM) in the DRL product formulation (b) (4) when compared to Imitrex nasal spray. As the pharmacokinetic profile of the DRL product is more like that of an injectable product, DRL references GSK's NDA 20080 (Imitrex Injection) to support approval under 505(b)(2).

¹ Systematic name: Dodecyl-4-O-α-D-glucopyranosyl-β-D-glucopyranoside. Also known as 1-O-n-Dodecyl-β-D-maltopyranoside.

B. Quality Assessment Overview

Drug Substance

Sumatriptan is a well-characterized small molecule that is approved under multiple NDAs and ANDAs. Information regarding manufacture and control of the bulk drug substance is incorporated by cross-reference to DMF (b) (4) (b) (4), Sumatriptan USP). 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.

Product

The proposed product is a unit dose nasal spray system that delivers 10 mg sumatriptan in 100 µL of a buffered aqueous solution containing (b) (4) DDM as a (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. (b) (4) 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 is (b) (4) (b) (4) that has not previously been used in any FDA-approved drug (b) (4) (b) (4). 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 DRI and the DMF Holder (b) (4)

The device component of the product is a (b) (4) from (b) (4). 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 (b) (4) (b) (4) (b) (4) All manufacturing steps are straight-forward and supported by the information in the application. (b) (4) (b) (4) 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. Justification for omitting other tests, such as viscosity and leachables was provided. It is noted that the Agency agreed at the pre-NDA meeting tha

(b) (4)

(b) (4)

(b) (4) After further consideration, the Agency requested that the application included testing at 0, 12, 24, and 36 months in the post-approval stability protocol for the first three commercial batches. The applicant agreed and amended the post-approval stability commitment accordingly.

Expiration Dating

The applicant requests a 36-month expiration dating period for the product when stored at controlled room temperature. Based on evaluation of the real-time data provided, the requested 36-month expiry is granted.

Facilities

All facilities that will be involved in commercial manufacture and testing of sumatriptan and sumatriptan nasal spray are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31 (b). The expected introduction concentration (EIC aquatic), is significantly below 1 ppb. The applicant states that, to their knowledge, no extraordinary circumstances exist. Thus, the claim for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment for Tosymra (sumatriptan) Nasal Spray

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach ^{(b) (4)}	Final Risk Evaluation	Comments
Sumatriptan assay, stability	Formulation, raw materials, moisture, air, container closure, process parameters, scale, equipment (excipient reactions, oxidation, hydrolysis)	L	(b) (4)	Adequate	Confirmed by stability data through 36 months at controlled room temperature.
DDM assay and stability	Formulation, raw materials, moisture, air, container closure, process parameters, scale, equipment (excipient reactions, oxidation, hydrolysis)	L		Adequate	Confirmed by stability data through 36 months at controlled room temperature.
Sumatriptan and DDM Spray Content/Dose uniformity	Formulation, filling process, device performance parameters	L		Adequate	The product is a solution thus risk mitigation approach applies to both components.
Droplet size distribution (DSD)	Device/actuator. viscosity	L		Adequate	
Leachables / Extractables	Formulation, container/closure, device	M		Adequate	
Biocompatibility	Pump component materials	L		Adequate	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Microbial limits	Formulation, raw materials, process parameters, moisture, container closure (packaging defects)	L	(b) (4)	Adequate	(b) (4)
Foreign matter	Particulates from excipients, equipment (b) (4), and other device components	L	(b) (4)	Adequate	

E. Lifecycle Management

Due to deficiencies in DMF (b) (4) DRL commits t (b) (4) The remaining DMF deficiencies are minor and should be addressed quickly. It is anticipated that, if the NDA is approved during this review cycle, (b) (4)



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LABELING

I. Package Insert – submitted 27Mar2018

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	DFN-02 (sumatriptan) Nasal Spray
Dosage form, route of administration	<i>Revision: Update with tradename Tosymra throughout labeling</i>
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Nasal Spray, 10 mg

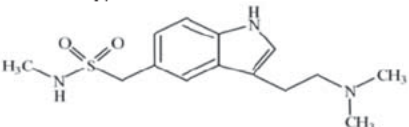
2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The recommended dose of DFN-02 is 10 mg given as a single spray in 1 nostril.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Unit dose nasal spray device delivering 10 mg of sumatriptan.
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	No information. <i>Revision: Add detailed description.</i>

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	DFN-02 contains sumatriptan, a selective 5-HT _{1B/1D} receptor agonist.
Pharmacological/ therapeutic class	
Dosage form and route of administration	No information. <i>Revision: Add dosage form and route of administration.</i>
Active moiety expression of strength with equivalence statement (if applicable) For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each 100 uL of DFN-02 contains 10 mg of sumatriptan USP in unit dose aqueous buffered solution containing citric acid monohydrate USP, potassium phosphate monobasic NF, sodium phosphate dibasic anhydrous USP, (b) (4), (b) (4), sodium chloride USP in water for injection, USP. (b) (4)
Chemical name, structural formula, molecular weight	[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulfonamide, and it has the following structure:  The empirical formula is C₁₄H₂₁N₃O₂S, representing a molecular weight of 295.40.
Other important chemical or physical properties (such as pKa or pH)	Sumatriptan is a white to pale yellow powder that is very slightly soluble in water. DFN-02 is a clear, pale yellow to yellow colored liquid. The pH range of solution is approximately 5.0 to 6.0 and the osmolality is between 270 to 330 mOsmol.

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	DFN-02 10 mg (NDC 67857-812-62)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	contains sumatriptan and is supplied as a clear pale yellow to yellowish liquid, in a ready-to-use, single dose, disposable unit.
Available units (e.g., bottles of 100 tablets)	Each carton contains 6 units (NDC 67857-812-61) and a Patient Information and Instructions for Use leaflet.
Special handling (e.g., protect from light)	(b) (4). <i>Revise to match container/carton labels: "Do not store in the refrigerator or freezer." "Do not test before use."</i>
Storage conditions	Store between 20°C and 25°C (68°F and 77°F). Excursions permitted between 15°C and 30°C (59°F and 86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Dr. Reddy's Laboratories Limited Distributed by: Promius Pharma, LLC, Princeton, NJ 08540

6. Patient Information

Information Provided in NDA	
How should I store DFN-02?	Store between 68° and 77°F (20° and 25°C) (b) (4) <i>Revise to match container/carton labels: "Do not store in the refrigerator or freezer." "Do not test before use."</i>
What are the ingredients in DFN-02?	Active ingredient: sumatriptan Inactive ingredients (b) (4) citric acid monohydrate, potassium phosphate monobasic, sodium chloride, sodium phosphate dibasic anhydrous in water for injection. (b) (4)
Manufactured for:	Dr. Reddy's Laboratories Limited
Distributed by:	Promius Pharma, LLC, Princeton, NJ 08540

Reviewer's Assessment of Package Insert: Adequate, pending the applicant's acceptance of the revisions noted above in red.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container (device and blister) labels	Information provided in the carton labels
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TOSYMRA™ (sumatriptan nasal spray)	
Dosage strength	10 mg	
Net contents	Each unit dose contains 10 mg of sumatriptan in 0.1 mL.	Each unit dose contains 10 mg of sumatriptan in 0.1 mL. This box contains six (6) unit dose nasal spray devices.
“Rx only” displayed prominently on the main panel	Present	
NDC number (21 CFR 207.35(b)(3)(i))	NDC 67857-812-62	NDC 67857-812-61
Lot number and expiration date (21 CFR 201.17)	Present	Present (bottom panel)
Storage conditions	Store between 20° C to 25° C (68° F to 77° F), excursions permitted 15° C to 30° C (59° F to 86° F). [See USP Controlled Room Temperature]. Do not store in the refrigerator or freezer.	
Bar code (21CFR 201.25)	Present	Present (back panel)
Name of manufacturer/distributor	Distributed by: Promius Pharma, LLC, Princeton, NJ 08540 Manufactured for: Dr. Reddy’s Laboratories Limited	
Special instructions	1 spray per unit. Do not test before use.	1 spray per unit. Do not test before use.

Reviewer’s Assessment of Labels: *Adequate*

List of Deficiencies: none



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MICROBIOLOGY[IQA Review Guide Reference](#)**Product Background:**

NDA: 210884

Drug Product Name / Strength: Sumatriptan Nasal Spray, 10 mg

Route of Administration: Nasal

Applicant Name: Dr. Reddy's Laboratories Limited

Manufacturing Site [REDACTED] (b) (4)

Method of Sterilization: Not applicable; the drug product is nonsterile

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The drug product is a 10 mg single-use, disposable unit. The drug product is nonsterile [REDACTED] (b) (4)

[REDACTED]. The application is recommended for approval.

List Submissions Being Reviewed: 3/27/2018, 6/15/2018, 7/19/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is an eCTD submission. The drug product is a new dosage form of sumatriptan for the treatment of migraine in adults.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): 0

S Drug Substance

Not applicable; the drug product is nonsterile.

P.1 Description of the Composition of the Drug Product

(Module 3.2.P.1, Description and Composition of the Drug Product.pdf)

- **Description of drug product** – clear pale yellow to yellow colored liqui (b) (4)

- **Drug product composition** –

Ingredient	Function	Unit (mg/0.1 mL)
Sumatriptan	Active ingredient	10
Citric acid monohydrate	(b) (4)	(b) (4)
Potassium phosphate monobasic		
Sodium phosphate dibasic anhydrous		
1-O-n-Dodecyl-β-D-maltopyranoside		
Sodium chloride		
Water for Injection		

- **Description of container closure system** –

Component	Description	Manufacturer
(b) (4)	Unit-Dos (b) (4) (b) (4)	(b) (4)

Reviewer's Assessment: *Adequate*

The applicant provided an adequate description of the drug product's composition and container closure system.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Not applicable; drug product is nonsterile. Therefore, CCIT is not assessed.

(b) (4)

Reviewer's Assessment: *Adequate*

The applicant has met regulatory expectations for USP <62> method suitability testing, including (b) (4) for a nonsterile drug product.

P.7 Container Closure**Summary table of the container closure system proposed****Reviewer's Assessment: See Section P.1****P.8 Stability****P. 8.1 Stability Summary and Conclusion**

(Module 3.2.P.8.1, Stability Summary and Conclusion.pdf)

Proposed expiry: 36 months at 20-25°C; excursions permitted to 15-30°C.

In the Information Request dated 07 June 2018, the following deficiency was issued:

(b) (4)

Reviewer’s Assessment: Adequate

The drug product is a unit dose formulation

(b) (4)

(b) (4)

P. 8.2 Post-Approval Stability Protocol and Stability Commitment
(Module 3.2.P.8.2, Post-approval Stability Protocol and Stability Commitment.pdf)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Microbial Limits Testing	USP <61> and <62>; complies with USP <1111>	(b) (4)

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25 ± 2°C/60 ± 5% RH

Test	Time (Months)							
	0	3	6	9	12	18	24	36
Microbial contamination	X		X		X		X	X

Post Approval Stability Commitment

The applicant commits to placing one batch in the stability program every year.

Reviewer’s Assessment: Adequate

The applicant provided stability data up to 36 months for two registration batches, and up to 24 months for one registration batch (the 36 month stability data will be updated during the review period). The applicant has met regulatory expectations regarding the design of the stability testing program to support the drug product’s microbiological quality throughout its shelf life.

P.8.3 Stability Data

(Module 3.2.P.8.3, Stability Data.pdf)

Long-term stability and accelerated studies were performed for lots 400869, 401349, and 401350. The provided results were acceptable.

Reviewer’s Assessment: Adequate

The stability data submitted to date support the microbiological quality of the subject drug product.

A Appendices

A.2 Adventitious Agents Safety Evaluation

(Module 3.2.A.2, Adventitious Agents Safety Evaluation – Manufacturer.pdf)

The applicant included CoAs for raw materials and primary packaging components that certify that the materials are free of TSE and BSE.

Reviewer's Assessment: *Adequate*

The applicant has met regulatory expectations for the evaluation of raw materials and packaging components for contamination with TSE and BSE.

R Regional Information

Executed Batch Records

(Module 3.2.R. Regional Information)

Executed batch records were provided for lots 400869, 401349, and 401350.

Reviewer's Assessment: *Adequate*

The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols

(Module 3.2.R., Comparability Protocol.pdf)

Not applicable.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Module 1.14.1.2, Annotated Draft Labeling Text.pdf)

The drug product is a ready-to-use, single dose, disposable unit nasal spray (10 mg); the recommended dose is 10 mg given as a single spray in one nostril.

Reviewer's Assessment: *Adequate*

The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments:

Reviewer's Assessment: Not applicable.

List of Deficiencies: Not applicable.

Primary Microbiology Reviewer Name and Date: Laura R. Wasil, Ph.D.; 26 July 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Erika Pfeiler, Ph.D.; 26 July 2018



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Heimann

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