

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210884Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 14, 2019

To: William Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): TOSYMRA (sumatriptan)

Dosage Form and Route: nasal spray

Application
Type/Number: NDA 210884

Applicant: Dr. Reddy's Laboratories, Inc.

1 INTRODUCTION

On March 27, 2018, Dr. Reddy's Inc., submitted for the Agency's review an Original 505(b)(2) New Drug Application (NDA) for sumatriptan nasal spray. The Applicant is seeking FDA approval for prescription marketing of the drug product for the treatment of adults with acute migraine with or without aura.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on April 11, 2018 for DMPP and OPDP to review the Applicant's proposed PPI and IFU for TOSYMRA (sumatriptan), nasal spray.

2 MATERIAL REVIEWED

- Draft TOSYMRA (sumatriptan) PPI and IFU received on March 27, 2018, and received by DMPP and OPDP on January 8, 2019.
- Draft TOSYMRA (sumatriptan) Prescribing Information (PI) received on March 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 8, 2019.
- Approved comparator labeling IMITREX (sumatriptan) nasal spray dated December 14, 2017.
- Approved comparator labeling ONZETRA XSAIL (sumatriptan succinate) inhalation powder dated January 27, 2016.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labelings where applicable.

4 CONCLUSIONS

- The PPI is acceptable with our recommended changes.
- The IFU is acceptable as submitted.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON W WILLIAMS
01/14/2019 10:02:31 AM

DHARA SHAH
01/14/2019 10:14:48 AM

LASHAWN M GRIFFITHS
01/14/2019 10:20:07 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: January 11, 2018

To: Heather Fitter
Division of Neurology Products (DNP)

Michelle Mathers, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for TOSYMRA (sumatriptan) nasal spray

NDA: 210884

In response to the DNP consult request dated April 11, 2018, OPDP has reviewed the proposed product labeling (PI), Patient Information, Instructions for use (IFU), and carton and container labeling for the original NDA submission for TOSYMRA (sumatriptan) nasal spray (Tosymra).

PI: OPDP's comments on the proposed labeling are based on the draft PI received from DNP (Michelle Mathers) on January 8, 2019 and are provided below.

Patient Information and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed patient labeling will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 9, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DHARA SHAH
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OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date	11/26/2018
To	Dahlia Walters, Project Manager OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	OPQ/OPRO
From	Marc Neubauer CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission # NDA 210884 ICCR #2018-02897 ICC#1800318
Recommendation	Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table

Reviewer	 Digitally signed by Marc S. Neubauer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, o.9.2342.19200300.100.1.1=2001712033 Date: 2018.12.06 08:12:56 -05'00'
Team Lead	 Sarah B. Mollo -S Digitally signed by Sarah B. Mollo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah B. Mollo -S, o.9.2342.19200300.100.1.1=2001712033 Date: 2018.12.06 09:28:46 -05'00'
Branch Chief	 Alan M. Stevens -S

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR #2018-02897
ICC tracking # (Lead)	ICC#1800318
Submission Number	NDA 210884
Sponsor	Dr. Reddy's laboratories, Inc.
Drug/Biologic	Sumatriptan Nasal Spray
Indications for Use	Treatment of migraine with or without aura
Device Constituent	Nasal Spray Device
Related Files	ICC 108088

Table 3. Important Dates	
Final Lead Device Review Memo Due	12/10/2018

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2. PURPOSE/BACKGROUND

2.1. Scope

CDER requested “Seeking an engineer review to evaluate the nasal spray.”

This consult involves a review of the essential performance requirements, design verification, design validation, stability, shipping validation, risk analysis and finished product specifications. It does not involve a review of biocompatibility or human factors since CDER reviewed this information.

2.2. Prior Interactions

CDRH consulted on IND 108088 and answered questions regarding essential performance requirements, design verification, and stability testing.

2.2.1. Related Files

2.3. Indications for Use

Combination Product	Indications for Use
Sumatriptan Nasal Spray	Treatment of migraine with or without aura
Nasal spray	Delivery of drug product

3. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

DFN-02 is a clear pale yellow to yellow colored liquid containing sumatriptan (10 mg/0.1 mL (b) (4)) (b) (4)

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) uL of (b) (4) 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.

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.

The following device information was found in 2.3.P Drug Product, Pages 36 - 38.

Nasal Spray Device

DFN-02 uses a unit dose nasal spray device (b) (4). 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).

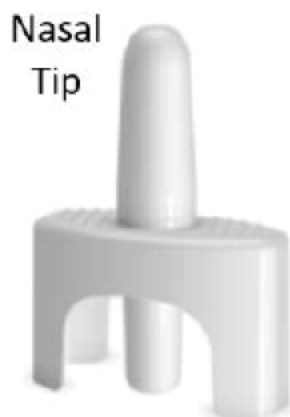
ICC#1800318

NDA 210884, Sumatriptan Nasal Spray

Dr. Reddy's Laboratories, Inc.

The complete assembly of the DFN-02 spray product is shown in Figure 2.3.P.7-1. Note that the component colors shown in cross-section image below are for illustrative purposes only.

Figure 2.3.P.7-1: Fully Assembled DFN-02 Device



(b) (4)

Device Components

DFN-02 nasal spray device consists of the following subassemblies and subcomponents:

(b) (4)

Table 2.3.P.7-3: List of DFN-02 Device Components

Sub-Component Name	Material of Construction	Color	Supplier
(b) (4)			

Please refer to Section 3.2.P.7 for the information on sequence of operation of DFN-02 device, overview of cGMP compliance and quality systems, design verification results and the risk management program for the DFN-02.

Essential Performance Requirements for the device found in the table below were found in 2.3.P Drug Product, Pages 10 – 12.

2.3.P Drug Product

Quality attributes of drug product	Target	Is it a CQA?	Justification
Microbial limits	Meets USP<61>, <62> and <111>	Yes	Noncompliance for microbial limits will impact the product quality and ultimately patient safety. Batches are manufactured according to cGMP using quality management system and compliance to microbial limits is demonstrated at release and through the shelf-life of the drug product.
Particulate matter (b) (4)	i) Not more than (b) (4) particles per mL ii) Not more than (b) (4) particles per mL iii) Not more than (b) (4) particles per mL	Yes	For patient safety and pharmacopoeial requirement
Deliverable volume	The delivered volume of spray should be between (b) (4) and the mean volume should be between (b) (4)	Yes	The amount of drug delivered is crucial in ensuring clinical performance of the product and to meet sumatriptan nasal spray USP monograph.
Delivered-Dose Uniformity for sumatriptan (Spray Content Uniformity)	Not more than one determination should be outside the range of (b) (4) of the label claim; None should be outside the range of (b) (4) of the label claim, and the mean should be within the range of (b) (4) of label claim (n = 10). If the above criterion is not met, select 20 additional devices, then Not more than three determinations should be outside the range of (b) (4) of the label claim; None should be outside the range of (b) (4) of the label claim, and the mean should be within the range of (b) (4) of label claim.	Yes	Variability in delivered dose uniformity of drug substance in product could compromise the safety and efficacy of the product and also to meet "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation". The same will be monitored during drug product release.

Quality attributes of drug product	Target	Is it a CQA?	Justification
Delivered-Dose Uniformity for DDM (Spray Content Uniformity)	Not more than one determination should be outside the range of (b) (4) of the target concentration of DDM. None should be outside the range of (b) (4) % of the target concentration of DDM, and the mean should be within the range of (b) (4) % of the target concentration of DDM. If the above criteria is not met, select 20 additional devices, then Not more than three determinations should be outside the range of (b) (4) of the target concentration of DDM. None should be outside the range of (b) (4) to (b) (4) of the target concentration of DDM, and the mean should be within the range of (b) (4) to (b) (4) of the target concentration of DDM.	Yes	Variability in delivered dose uniformity of DDM in the product will affect the sumatriptan absorption and could compromise the safety of the patients. The same will be monitored during drug product release.
Droplet Size Distribution ≤10 µm DV10 DV50 DV90 Span ^a	Not more than (b) (4) Not more than (b) (4) Not more than (b) (4) Not more than (b) (4) Between (b) (4)	Yes	Variation in the droplet size distribution may influence the nasal deposition pattern of sprays and thus may compromise the safety and efficacy.
Spray pattern and Plume Geometry a) Dmin b) Dmax c) Ovality ^b d) Plume angle	a) Not less than (b) (4) b) Not more than (b) (4) c) Between (b) (4) d) Not more than (b) (4)	Yes	The spray pattern and plume geometry would indicate product quality.

Quality attributes of drug product	Target	Is it a CQA?	Justification
e) Plume width	e) Not more than (b) (4) mm		

^a Span = [(DV90- DV10) / DV50]

^b Ovality = Dmax / Dmin

* Formulation and process variables are unlikely to impact these CQAs. However, these CQAs remain a target element of the QTTP.

Reviewer's Comments

CDRH was consulted on IND 108088 and answered questions regarding essential performance requirements. The firm has followed our advice from IND 108088. IR Request #1 was sent for EPRs because 1) they need to justify why the actuation force has an upper specification limit of (b) (4) they need to clarify why they are using a volume unit for their spray weight specification (see Deficiency #1 below). The sponsor clarified the upper limit for actuation force is (b) (4) and they provided adequate justification for this specification in their response. They also clarified their weight loss specification is used to analyze their stability testing. Their response is adequate.

4. DESIGN VERIFICATION AND VALIDATION REVIEW

4.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing			x
To-be-marketed device was used in the pivotal clinical trial			x
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			x
Traceability demonstrated for specifications to performance data	X		

4.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device			x
Bioequivalence Study utilized to-be-marketed device			x
Simulated Actual Use Study utilized to-be-marketed device			x

The following information was found in Container Closure System located in 3.2.P.7.

Human Factors

Design Validation is not required for DFN-02 as agreed with the FDA in [communication dated 16 November 2017](#).

The DFN-02 Unit dose nasal spray device is similar to several marketed products (e.g. Narcan®, Imitrex®, Zomig®). The device constituent parts for each of the referenced products as well as DFN-02 are (b) (4). (b) (4) DRL 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 determined that DFN-02 does not introduce any new risks into the market place, hence not requiring further human factors validation. Our conclusion is justified based on the following evaluations:

A. Product Safety communications and Adverse event reports:

DRL researched public sources for any product safety communication and adverse event report and did not find any information regarding new or unique risks associated with the use of the proposed device. The search included the following databases:

- MAUDE Database - Manufacturer and User Facility Device Experience
- MedSun Database - Medical Product Safety Network
- Literature

B. Device & User data from DFN-02 Clinical Studies: DFP-02-CD-010 & DFP-02-CD-012 DRL conducted two clinical studies using the unit dose nasal spray device for DFN-02, (Study DFP-02-CD-010 and DFP-02-

CD-012). A total of 3,481 DFN-02 devices were used (self-administered) by 260 patients. No user or device failures were reported during these clinical studies. The study reports for these studies will be included in the NDA for DFN-02.

C. DFN-02 Nasal Spray vs. Imitrex Nasal Spray: [Comparative Analyses](#)

DRL performed comparative analyses such as a labeling comparison, comparative task analysis, and physical comparison between DFN-02 Nasal Spray and the Imitrex Nasal Spray to evaluate if there are any differences exist between the user interfaces and where the same or similar risks may apply to DFN-02.

Based on the comparative analyses and formative study, DRL concluded that the proposed DFN-02 Nasal Spray instructions for use, labeling and packaging are essentially identical to the marketed Imitrex Nasal Spray. Further, DFN-02 Nasal Spray is also comparable to another marketed nasal spray for migraines (Zomig® Nasal Spray) and identical to an opioid overdose nasal spray (Narcan® Nasal Spray). In summary, DFN-02 Nasal Spray is comparable to existing approved nasal sprays, two of which are for the same indication and same intended users.

D. [DFN-02 Application Failure Mode and Effect Analysis \(aFMEA\)](#)

DRL has performed an aFMEA for the DFN-02 nasal spray with the proposed Instructions for Use (user steps) and concluded that there are no residual risks associated with the device design, packaging, or instructions that would lead to failures, high risk errors, or patient safety issues.

The [proposed IFU](#) and [carton labeling](#), includes the suggested changes included in the FDA communication dated 16 November 2017.

4.3. Design Verification Review

The following traceability information is found in the document, Essential Performance Requirement Traceability Matrix in Section 3.2.P.7 Container Closure System.

The objective of the traceability matrix is to ensure all the essential performance requirements of the DFN-02 device constituent part have been adequately verified and validated.

(b) (4)

1. Design Validation is not required for DFN-02, as proposed and agreed by the FDA in communication dated 16 November 2017. However, DRL monitored device use across two clinical studies, in which a total of 3481 devices were used by 260 subjects. There were no nasal spray device malfunctions or failures, no packaging or labeling failures reported or observed during the clinical studies.
2. Based on the FDA Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation", Dr Reddy's has tested plume geometry (b) (4)
(b) (4)
3. (b) (4). The data is submitted to FDA as part of the design verification report. In accordance with the Guidance, DRL does not intend to test plume geometry as part of commercial release. This approach was discussed with FDA in pre-NDA meeting dated 13 Dec, 2017.
3. The DFN-02 nasal spray is a mono-dose device filled with solution formulation. Once the content uniformity of sumatriptan is established at release testing, the content uniformity during stability in the device would remain constant as the device contains formulation sufficient for a single dose. Deliverable volume performed during stability will ensure the delivery of required dose from the device and spray content uniformity testing would not yield any additional information during stability. Hence, spray content uniformity for sumatriptan test parameter included only during release testing. The above approach was agreed with FDA in the request for guidance meeting dated April 23, 2014.
4. Actuation force, being a device- specific performance parameter, will be tested (b) (4)
(b) (4) as agreed with FDA during pre-NDA meeting dated 13 Dec, 2017.

The sponsor provided their design verification and stability results in the document, Design Verification Report, located in Section 3.2.P.7. They tested the following lots and aging conditions:

- Table 2a Summary of Functional Performance of Lot 400869, Upright Orientation
- Table 2b Summary of Functional Performance of Lot 400869, Horizontal Orientation
- Table 2c Summary of Functional Performance of Lot 401349, Upright Orientation
- Table 2d Summary of Functional Performance of Lot 401349, Horizontal Orientation
- Table 2e Summary of Functional Performance of Lot 401350, Upright Orientation
- Table 2f Summary of Functional Performance of Lot 401350, Horizontal Orientation

The sponsor provided their shipping validation results in the document, Transportation Validation – Shipping Study Report, located in Section 3.2.P.7.

Reviewer's Comments

The sponsor's data for design verification and stability testing of their essential performance criteria all passed their acceptance criteria. There was one protocol deviation which was found acceptable and did not affect the validity of the results. They tested two lots and for both lots they tested in the horizontal and upright orientation.

In their original submission, the sponsor did not provide their 36-month testing. **IR Request #1** was sent on 6/14/2018 (see Deficiency #2 below). The sponsor provided their 36-month data. All samples passed. Their response is adequate.

During the final review of this submission, it was noticed that the sponsor did not include actuation force in their stability testing. On 12/3/2018, the following IR comment was sent: Actuation force should be included in the commercial drug product stability specification. Update section 3.2.P.8.2 and other relevant sections. CDER will review this IR when it comes back since it is a protocol update.

For shipping validation, the sponsor performed a visual inspection and tested the following functional requirements: droplet size distribution, plume geometry results, spray pattern results and deliverable volume. Their sample size was adequate. However, they did not test activation force or provide a justification why they did not. **IR Request #1** was sent on 6/14/2018 (see Deficiency #3 below). The sponsor provided shipping testing with actuation force. Their response is adequate.

5. RISK ANALYSIS

5.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

Reviewer's Comments

The sponsor provided a use FMEA for their device in the original submission. They did not provide a design FMEA analysis that would consider hazards such as overdose, under dose, and delay of treatment. As a response to IR Request #1 the sponsor provided a design FMEA document for the combination product. Their risk analysis is adequate (see Deficiency #4 below).

6. FINAL RELEASE SPECIFICATIONS

The table displayed in Section 4.3 of this memo shows the final release specifications. They are the same as the specification listed under the design outputs. The only design output that will not be tested during final release is plume geometry. No deficiencies were noted.

7. LABELING

This labeling information was taken from their aFMEA report because it was in a convenient format. The report was located in Section 3.2.P.7.

8. COMPLIANCE REVIEW

Since this nasal spray does not have unique features or being used in emergency situations, a GMP inspection is not recommended.

The sponsor has chosen a streamline adherence to the 21 CDR 820 regulations under 21 CFR Part 4.4. Installation and Servicing procedures are not applicable. An IR request was sent on 10/29/2018, requesting the sponsor's management control, CAPA, design control, and purchasing control procedures. The sponsor provided these procedures and no deficiencies were noted. See checklist below.

1. Was the last inspection OAI?	YES ☐	NO ☒	
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☐	NA ☒
3. Is the combination product meant for emergency use?	YES ☐	NO ☒	
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☐	NO ☒	
5. Does the firm have a known history of multiple class I recalls, repeat class II recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	NA ☐
6. Would withholding approval of the finished combination product create a shortage?	YES ☐	NO ☐	UNK ☒

7. Was the last inspection VAI?	YES ☐	NO ☒	
8. Has the firm not had any previous inspections?	YES ☒	NO ☐	
9. Is the combination product meant for home use, hospital use, or military use?	YES ☒	NO ☐	
10. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	
11. Does the firm have a known history of class II recalls, MDRs/AEs, or VAI inspections?	YES ☐	NO ☒	NA ☐

12. Management Control, 21 CFR 820.20 The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES ☒	NO ☐	NA ☐
13. The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES ☒	NO ☐	NA ☐
14. Design Control, General, 21 CFR 820.30 The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES ☒	NO ☐	NA ☐
15. The procedures description includes how requirements for each of the following are fulfilled. a. Design and Development Planning	YES ☒	NO ☐	NA ☐
b. Design Input	YES ☒	NO ☐	NA ☐
c. Design Output	YES ☒	NO ☐	NA ☐
d. Design Review	YES ☒	NO ☐	NA ☐
e. Design Verification	YES ☒	NO ☐	NA ☐
f. Design Validation	YES ☒	NO ☐	NA ☐
g. Design Transfer	YES ☒	NO ☐	NA ☐
h. Design Changes	YES ☒	NO ☐	NA ☐
i. Design History File	YES ☒	NO ☐	NA ☐
16. The firm provided a copy or a summary of the plan used to design the combination product.	YES ☒	NO ☐	NA ☐
17. Purchasing Controls, 21 CFR 820.50 The sponsor firm should summarize its procedure(s) for purchasing controls.	YES ☒	NO ☐	NA ☐
18. The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES ☒	NO ☐	NA ☐

19. The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES ☒	NO ☐	NA ☐
20. The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES ☒	NO ☐	NA ☐
21. The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES ☒	NO ☐	NA ☐
22. The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES ☒	NO ☐	NA ☐
23. Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES ☒	NO ☐	NA ☐
24. The CAPA system should require:	YES ☒	NO ☐	NA ☐
a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;			
b. Investigation of nonconformities and their causes;	YES ☒	NO ☐	NA ☐
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES ☒	NO ☐	NA ☐
d. Verification or validation of the actions taken.	YES ☒	NO ☐	NA ☐
25. Installation, 21 CFR 820.170 (check NA if Installation is not required for this combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES ☐	NO ☐	NA ☒
26. Servicing, 21 CFR 820.200 (check NA if Servicing is not required for this combination product) Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.	YES ☐	NO ☐	NA ☒

9. INTERACTIVE REVIEW

Agency Information Request #1 (sent on 06/14/2018) - ADEQUATE

Sponsor Response (received on 06/28/2018)

- 1) In your document, 3.2.P.7 Container Closure System, you defined your essential performance requirements. Address our following concerns:
- Your actuation force is (b) (4). Provide a justification why the specification range is (b) (4). Provide literature or testing that all segments of your intended use population (i.e. elderly females) can apply a force of (b) (4). If your research determines this is not the case, redefine your actuation force specification and ensure your design verification, shipping validation and stability data support it.

Dr. Reddy's Response:

Dr. Reddy's would like to clarify that the actuation force specified in Table 3.2.P.7.2-4 in Section 3.2.P.7 (Sequence 0000) was incorrect. The actuation force was inadvertently represented as (b) (4) instead of (b) (4). Dr. Reddy's hereby confirms that the actuation force for DFN-02 is (b) (4) and Table 3.2.P.7.2-4 in Section 3.2.P.7 have been updated accordingly and included with this amendment.

The unit dose device actuation force range (b) (4) was established and justified by the manufacturer of the device (b) (4) based on the following factors and benefits:

- A lower limit for actuation force that is intended to prevent unintentional actuation, while at the same time ensure that a desired threshold pressure is applied to break the "safety features" (bridges) in order to actuate the device and deliver the spray
- An acceptable upper limit of actuation force is based on (b) (4) experience from nasal spray devices already in the market that have been used in a broad spectrum of patient population in multiple therapeutic indications including migraine.

The Unit dose nasal spray device used in DFN-02 has been approved for commercial use of products such as Narcan®, Nascobal®, generic Sumatriptan nasal products, etc (b) (4) and has not introduced any design changes in the device.

An independent search from both (b) (4) and Dr. Reddy's through different public sources for product safety communication and adverse events showed no evidence of new or unique risks or complaints associated with the use or actuation of the proposed unit dose device. The search was performed in the following databases:

- FDA's MAUDE Database - Manufacturer and User Facility Device Experience
- FDA's MedSun Database - Medical Product Safety Network

Further, DFN-02 study data, as noted below, confirms patient ability to use and actuate the device without any failure or difficulty:

- DFN-02 Formative study:** This study included 8 participants, all of whom dosed successfully and easily and none of whom expressed any difficulty in dosing. All participants were true migraine sufferers of 21-56 years old (5 female, 3 male, and a wide range of ethnicity).
- DFN-02 Clinical Studies:** Dr. Reddy's conducted two clinical studies using the proposed unit dose nasal spray device, Study # DFP-02-CD-010 and Study# DFP-02- CD-012. A total of 3,481 DFN-02 devices were used (self-administered) by 260 migraine patients (19-68 years old, 211 females, 49 males, and wide range of ethnicity). No user or device failures were reported during these clinical studies.

As described in the memo from (b) (4) (b) (4). The device is used across multiple therapeutic areas and different products

listed in (b) (4) memo and only one (1) complaint was received over the last five (5) years from an impaired patient with arthritis related to improper actuation (b) (4); memo also indicates that no complaints were reported for actuation force from migraine patients.

Based on the clinical studies conducted with DFN-02, customer complaint data, market information from current approved drugs using the same device and (b) (4); nasal spray device experience, the actuation force specification is justified for the intended application.

Reviewer Comments

The sponsor stated they inadvertently provided the wrong specification and the actuation force is (b) (4). They also provided adequate justification and test data to support this specification. Their response is adequate.

- b. On Page 13, Section 3.2.P.7.2.5.1 of 3.2.P.7 Container Closure System, you identify Pump Delivery (Spray Weight) as an essential performance requirement but you define your specification as Individual spray (b) (4) µl and Average of (b) (4) sprays (b) (4) µl. You also define a Weight Loss specification as NMT (b) (4) of total weight. Clarify why your Pump Delivery specification is in units of volume and not weight. Clarify if your Weight Loss specification is also an indication of Pump Delivery. If the Weight Loss specification is a part of Delivered Volume then this specification should be testing in your shipping validation and considered an essential performance requirement.

Dr. Reddy's Response:

The specifications including the units the pump delivery (Deliverable volume) for DFN-02 are defined according to USP monograph for Sumatriptan Nasal Spray.

(b) (4)
The specification and overall testing approach is in accordance with the USP monograph. The essential performance requirement for Pump Delivery (Spray Weight) included in Section 3.2.P.7.2.5.1 was revised to read Pump Delivery.

Dr. Reddy's confirms that Weight Loss specification is not an indication of Pump Delivery. Weight loss was measured to assess the weight loss on stability, as recommended in FDA's Guidance for Industry - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, 2002. Weight loss test assesses the sealing characteristics of the container closure system during stability, whereas pump delivery test assesses the pump-to-pump reproducibility of the delivered volume of spray. Therefore, weight loss specification is not part of pump delivery specification.

Reviewer Comments

The sponsor clarified their weight loss specification is not a part of their pump delivery specification. The weight loss specification is used for weight loss during stability to assess container closure integrity per FDA guidance. They also clarified their pump delivery specification. Their response is adequate.

- 2) You indicated you will provide the stability data for the 36-month timeframe at a later date. Provide the date when you think you will provide this information.

Dr. Reddy's Response:

The 36-month stability summary (Section 3.2.P.8.1) and stability data (Section 3.2.P.8.3) are included with this amendment.

Reviewer Comments

The sponsor provided their 36-month stability data. All data passed their acceptance criteria. Their response is adequate.

- 3) Your shipping validation study did not test actuation force, an essential performance requirement. Perform a shipping validation and ensure actuation force is tested. Note: the sample size for all essential performance requirements except activation force appear adequate when design verification, shipping and stability are looked at in total. When you perform this activation force testing, ensure you have adequate sample size taking all the testing into account.

Dr. Reddy's Response:

Dr. Reddy's agrees with the agency's recommendation and is in the process of generating actuation force test results as part of shipping validation.

We have retained samples from the shipping validation study provided in NDA. A total of 56 DFN-02 samples that have already undergone the ASTM 4169-D16 testing that are retained will be used to generate actuation force data. Dr. Reddy's commits to provide this report by first week of August 2018.

This response is a follow up to the commitment made to the agency in response to information request submitted on June 28, 2018 (Sequence 0006). Dr. Reddy's has performed actuation force testing as part of shipping validation. This submission includes the actuation force test report.

SUMMARY OF RESULTS

Results for Actuation force in Newtons (N) on the samples post transportation validation of lot 401350.

No of Samples Tested	56 units
Acceptance Criteria	(b) (4)
Average	(b) (4)
SD	
% CV	
Min	
Max	

Reviewer Comments

In a quality amendment dated 8/6/2018, the sponsor provided their shipping validation report where they tested the actuation force of the device. The sample size was adequate. All samples passed the acceptance criterion. Their response is adequate.

- 4) In your document, Application Failure Mode and Effects Analysis, DFN-02 Sumatriptan Unitdose Nasal Spray, Document No. PP-17-0011-00, is the device risk analysis document that you provided for this submission. This document is inadequate because it focuses primarily on the instructions for use and does not place enough

emphasis on the risks associated with the design of the device. Provide additional information on your FMEA to cover hazards such as under dose, overdose, delay of care, infection, etc. For example, delay of care can be associated with an actuation force that is too high for a particular segment of the population (i.e. elderly female). Additionally, provide how you are mitigating these hazards not just through labeling but also through design, verification, validation, manufacturing, etc.

Dr. Reddy's Response:

Dr. Reddy's acknowledges agency's comment regarding device risk analysis documentation related to DFN-02. In addition to DFN-02 Application FMEA previously submitted to agency, Dr. Reddy's has also performed design risk analysis on DFN-02 focused on design elements of the combination product. This design Failure Mode and Effects Analysis included with this submission (PP-18-0005-00) covered hazards related to device design, such as under dose, overdose, delay of care, infection etc. No unacceptable level of concern was identified with any of the failure modes identified, and there are no residual risks associated with the device or combination drug-device design, packaging or labeling that would lead to failures.

In addition to the DFMEA conducted by Dr. Reddy's, the device component manufacturer (b) (4). Details of this risk analysis conducted by (b) (4) are provided in their Drug Master File (DMF) # (b) (4); pages 676-734 as referenced in the letter of authorization included with the original NDA submission (sequence 0000).

Reviewer Comments

The sponsor provided a design FMEA I did not note any deficiencies. Their response is adequate.

Agency Information Request #1 (sent on 10/29/2018) - ADEQUATE

Sponsor Response (received on 11/2/2018)

- 1) In your document, 3.2.P.7 CONTAINER CLOSURE SYSTEM [SUMATRIPTAN NASAL SPRAY, 10 MG, (b) (4) Table 3.2.P.7.2.3 lists the DRL Procedures associated with cGMP compliance for combination products. You did not provide these procedures for our review. Provide the following procedures for our review:

(b) (4)

Dr. Reddy's Response:

Dr. Reddy's would like to clarify that since submission of NDA some of the requested procedures associated with cGMP compliance have been replaced and/or consolidated into new procedures as part of Quality System continuous improvement. During this process, additional procedures have been put in place.

Please refer to the table below for the list of requested procedures and the current procedures associated with cGMP compliance for combination products.

(b) (4)



The copies of the procedures that are currently effective for combination products referenced in the table above are provided in the submission.

In addition, 3.2.P.7, Container Closure System, Table 3.2.P.7.2-3 has been updated with the current SOPs as described in the table above and provided in this submission.

Reviewer Comments

The sponsor has chosen a streamline adherence to the 21 CDR 820 regulations under 21 CFR Part 4.4. Installation and Servicing procedures are not applicable. The sponsor provided the required procedures and no deficiencies were noted. See checklist in Section 9.

10. OUTSTANDING DEFICIENCIES

There are no outstanding deficiencies.

11.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable.



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 23, 2018.

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Ph.D., Director
Martin S. Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: **Product name:** DFN-02/DFP-02/Sumatriptan Nasal Spray 10 mg
NDA 210884
Trade Name, dosages, formulations, routes: Tosymra Intranasal.
Recommended dose: 10 mg given as a single spray in 1 nostril.
Maximum dose in a 24-hour period: 30 mg, separate doses by at least 1 hour
IND Number: 108088
Indication(s):
Acute treatment of migraine with or without aura (b) (4) in adults.
Sponsor: Dr. Reddy's Laboratories
PDUFA Goal Date: January 27, 2019

Materials Reviewed:

- 1.11.4 Abuse related information
- 2.3 Quality overall summary
- 2.6.2 Pharmacology written summary
- 2.7.4 Summary of Clinical safety
- 5.3.1., 5.3.5. Clinical study reports

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) dated April 6, 2018, to the Controlled Substance Staff (CSS) to evaluate abuse-related preclinical and clinical data submitted in NDA 210884 (developed under IND108088) for Sumatriptan Nasal Spray/ DFN-02/ DFP-02 (proposed trade name, Tosymra). The drug is indicated for the acute treatment of migraine with or without aura (b) (4) in adults. The recommended dose is 10 mg given as a single spray in one nostril. The drug product, DFN-02, is a unit-dose nasal spray device containing (b) (4) microliters of a (b) (4) mg/mL sumatriptan solution, (b) (4) of a novel excipient, 1-O-n dodecyl-β-D-maltopyranoside (DDM), and citric acid (b) (4) in an intended administration volume of 100 μL in a single spray to deliver a 10 mg dose intranasally. DDM belongs to a class of nonionic surfactants, and (b) (4). The Sponsor claims that its inclusion in DFN-02 enables sumatriptan to be absorbed faster, reaching therapeutic plasma C_{max} levels more rapidly than the subcutaneous injection of sumatriptan and uses a lower dose of sumatriptan than the highest dose of currently approved nasal formulations of sumatriptan (20 mg).

The current NDA is being submitted via the 505(b)(2) regulatory pathway and relies on clinical bridging though comparative bioavailability to the Listed Drug ([LD] Imitrex Injection, sumatriptan succinate, 6 mg).

Sumatriptan was approved in the U.S. in 1992 and is not a controlled substance under the Controlled Substances Act (CSA). Based on the safety profile of the LD and the lack of a signal for abuse in the clinical trials, the Sponsor concludes that DFN-02 does not require scheduling as a controlled substance.

2. Conclusions

1. The current NDA is being submitted via the 505(b)(2) regulatory pathway and relies on clinical bridging through comparative bioavailability to the LD, Imitrex Injection, (sumatriptan succinate, 6 mg).
2. Sumatriptan has been available in the US since 1992 and there is no evidence of its abuse noted in the scientific literature.
3. During clinical trials of sumatriptan nasal spray no abuse related AEs were reported.

3. Recommendations

1. Based on our findings, as captured in the Conclusions section, we agree with the Sponsor that sumatriptan nasal spray/ DFN-02/ DFP-02 (Trade name Tosymra) does not require scheduling under the CSA.
2. Section 9, Drug Abuse and Dependence, need not be included in the product label.

II. DISCUSSION

1. Chemistry

1.1 Substance and Product Information

Sumatriptan USP was used as the drug substance for development of DFN-02. Its chemical name is 1-[3-[2-(dimethylamino) ethyl]-1H-Indole-5-yl]-N-methylmethanesulfonamide. It is a white to pale yellow, non-hygroscopic powder that is very slightly soluble in water with a melting range between 169°C to 171°C.

DFN-02, developed by the Sponsor, is a drug device combination product intended for nasal administration comprising the active ingredient sumatriptan and 1-O-n-Dodecyl-β-D-Maltopyranoside (DDM). DDM is a novel excipient, (b) (4), which, according to the Sponsor, offers a favorable pharmacokinetic (PK) profile with a (b) (4). (b) (4) DDM is a (b) (4).

Sumatriptan nasal spray, 10 mg, is a clear pale yellow to yellow colored liquid containing sumatriptan (10 mg/0.1 mL), (b) (4). (b) (4)

The container closure spray device is a unit dose drug/device product. The device contains (b) (4) μL of a (b) (4) mg/mL aqueous buffered solution of sumatriptan and is designed to deliver a single dose/spray of 100 μL containing 10 mg of sumatriptan. The device would contain drug product sufficient for single administration with minimal residual volume that would not yield any deliverable dose post single use.

2. Nonclinical Pharmacology

Sumatriptan is a selective 5-HT_{1B} and 5-HT_{1D} receptor agonist first approved by the FDA in 1992. Several dosage forms of sumatriptan (subcutaneous injectable, oral tablet, nasal spray) are currently available in the market for the acute treatment of migraine with or without aura in adults (b) (4)

The Sponsor has not conducted any specific studies related to abuse potential in animals. Sumatriptan is structurally similar to serotonin (5-HT) and the therapeutic effects of sumatriptan are believed to be mediated through agonistic activity at the 5-HT_{1B/1D} receptors on intracranial blood vessels and sensory nerves of the trigeminal system. This results in cranial vessel constriction and inhibition of pro-inflammatory vasoactive neuropeptide release.

Effects on Central Nervous System (Protocol DFP-02_SE_01): The objective of this study was to determine potential effects of a single intranasal administration of DFN-02 on general activity, behavior and body temperature in the rat. Male Sprague Dawley rats (n = 6/group) were administered a single dose of DFN-02 at dose levels of 0 (vehicle control), 5, 10, and 15 mg sumatriptan/animal. The intranasal administration of single doses of DFN-02 at dose levels of 5, 10 and 15 mg sumatriptan/rat produced no behavioral, autonomic, or motor effects, and no biologically significant changes in body temperature in rats when compared to the vehicle control group.

3. Clinical Pharmacology

The pivotal Bioequivalence (BE) study DFP-02-CD-009, showed DFP-02 10mg is BE to the 4mg Imitrex dose. The elimination half-life of sumatriptan following administration of DFN-02 is 2.44 ± 1.00 hours.

4. Clinical Studies

The Sponsor conducted seven Phase 1 studies, one Phase 2, and one Phase 3 study in their clinical development program. Adverse events (AEs) were coded using MedDRA to classify events under primary system organ class (SOC) and preferred term (PT).

4.1 Adverse Event Profile Through all Phases of Development

Phase 1 studies: Seven Phase 1 studies were conducted on 190 healthy volunteers. The test formulation (5-20 mg doses) was compared with placebo, Imitrex nasal spray, or subcutaneous Imitrex injection. No abuse-related AEs were reported in any group.

Phase 2 and 3 Studies:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine with or Without Aura (Phase 2) Protocol DFN-02-CD-012.

This was a randomized, placebo-controlled, two double-blind (DB) treatment period study. Previously diagnosed subjects with a history of episodic migraine were randomized in a 1:1 ratio in each of the DB periods to receive either DFN-02 (sumatriptan nasal spray, 10 mg) or a matching placebo. Subjects treated one migraine attack with moderate to severe pain in the DB1 treatment period and, if eligible,

were re-randomized into the second DB treatment period (DB2) to treat another migraine attack at any pain level.

In DB1 50 subjects received DFN-02 and 43 subjects received placebo while in DB2, 37 subjects received DFN-02 and 38 received placebo. The most commonly reported AE was dysgeusia. No abuse-related AEs were reported.

A Multicenter, Open-label Safety Study of DFP-02 (10mg) for the Treatment of Acute Migraine in Patients with 2 to 6 Migraine Headaches a Month (Phase 3) Protocol DFP-02-CD-010.

This was an open-label, repeat-dose safety study conducted at multiple study centers. Previously diagnosed patients with acute migraine headaches were treated with intranasal DFP-02 (sumatriptan) 10 mg over the course of a 6-month period. A total of 173 patients were enrolled in the study, 167 patients received at least one dose of study drug, and 134 patients completed the study. The mean duration of patient enrolled in the study was 163 days (range 3-241 days).

The most commonly reported treatment emergent AEs (TEAE) overall ($\geq 5\%$) were dysgeusia (21.0%), application site pain (30.5%), application site reaction (5.4%), upper respiratory tract infection (10.8%), nasopharyngitis (7.2%), and sinusitis (6.6%). TEAE of ‘feeling jittery’ occurred in one patient leading to discontinuation from study medication. A total of 2 patients reported 16 events of ‘feeling jittery.’ No other abuse-related AEs were reported.

4.2 Safety Profile

During the Phase 1-3 studies on sumatriptan nasal spray, no abuse related AEs were reported. There were isolated reports of ‘feeling jittery’ which, in the absence of other stimulant-like AEs such as euphoria, restlessness, hypervigilance, increased energy, do not suggest abuse potential.

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There was no indication of abuse, misuse, or diversion during the clinical trials.

4.4 Tolerance and Physical Dependence Studies in Humans

Tolerance and physical dependence studies were not conducted. This is appropriate as there is no evidence of abuse potential and the drug is to be utilized episodically for the treatment of headaches.

5. Regulatory Issues and Assessment

Sumatriptan has been available in the U.S. since 1992 and there is no evidence of its abuse noted in the scientific literature. During clinical trials of sumatriptan nasal spray, no abuse-related AEs were reported. Thus, we agree with the Sponsor, sumatriptan nasal spray does not need to be controlled under the CSA. Section 9, Drug Abuse and Dependence, need not be included in the product label.

6. Other Relevant Information

In a study of 12 male subjects with histories of substance abuse (Sullivan JT et.al. 1992), sumatriptan in contrast to morphine, produced a dose-related decrease on euphoria scores, elevated scores on measures of apathetic sedation and disliking. This study confirms that sumatriptan has low abuse potential.

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/s/

SHALINI M BANSIL
11/23/2018

MARTIN S RUSINOWITZ
11/23/2018

DOMINIC CHIAPPERINO
11/23/2018

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 15, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210884
Product Name and Strength:	Tosymra (sumatriptan nasal spray) 10 mg
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
FDA Received Date:	October 9, 2018
OSE RCM #:	2018-816-2
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Tosymra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling for Tosymra are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Rider B. Label and Labeling Review for Tosymra (NDA 210884). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 26. RCM No.: 2018-816-1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIANA B RIDER
10/15/2018

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LOLITA G WHITE
10/15/2018

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 26, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210884
Product Name and Strength:	Tosymra (sumatriptan nasal spray) 10 mg
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
FDA Received Date:	August 31, 2018
OSE RCM #:	2018-816-1
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Tosymra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective because it is unclear whether the lot number and expiration date will be clearly differentiated from one another.

3 RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES LIMITED

We recommend the following be implemented prior to approval of this NDA:

^a Rider B. Label and Labeling Review for Tosymra (NDA 210884). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 12. RCM No.: 2018-816.

- A. We note the lot number and expiration date are denoted by a placeholder on the container labels and carton labeling and are in close proximity to each other. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend you consider adding the header Exp: for the expiration date and the header Lot: for the lot number to better differentiate this important information on the container labels and carton labeling.^b

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 31, 2018

Commercial Presentation

- Container label
- Blister labeling (Initial launch & proposed future)
- Carton labeling

Physician Sample

- Container label
- Blister labeling (Initial launch & proposed future)
- Carton labeling

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

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/s/

BRIANA B RIDER
09/26/2018

LOLITA G WHITE
09/26/2018