CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212157Orig1s000

OTHER REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 30, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products / CDER

To: Harold Sano, RPM
DNP

Subject: QT-IRT Consult to NDA # 212157 (SDN # 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 7/18/2019 regarding the Division's QT related question. The QT-IRT reviewed the following materials:

- Sponsor's request for TQT study waiver (SN0000 / SDN001; link);
- Sponsor's clinical study report # DFN-15-CD-008 (SN0000 / SDN001; link);
- Sponsor's propose product label (SN0000 / SDN001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002 / SDN003; link).

1 QT-IRT Responses

Question: The applicant requests a waiver for the need to conduct a clinical evaluation of the potential for DFN-15 to cause QT/QTc interval prolongation as per the ICH E14 Guidance (October 2005). The applicant states the basis for this waiver request is the known cardiovascular effects of celecoxib, the exposure of celecoxib at the recommended dose for DFN-15 of 120 mg/day for the current indication, and clinical safety data of DFN-15.

QT-IRT's response: Yes, we agree.

For 505(b)(2) regulatory pathway, a standalone thorough QT study is generally not required if the steady-state exposures (Cmax) of drug and its metabolites from the new formulation of an approved product at the highest therapeutic dose are not significantly higher than those for approved marketed product (reference listed drug) and the QT relevant sections of approved marketed product (reference listed drug) can be adopted for the new product label (ICH E14, section 1.3).

2 BACKGROUND

2.1 Product Information

Dr. Reddy's Laboratories Limited is developing a liquid formulation of celecoxib (Elyxyb®) for the acute treatment of migraine (with or without aura in adults) using a 505(b)(2) regulatory pathway. Celecoxib (MW: 381.4) is a nonsteroidal anti-inflammatory drug which is believed to inhibit prostaglandin synthesis by action on cyclooxygenase-2. It approved for management of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis (≥ 2 years), ankylosing spondylitis, acute pain, primary dysmenorrhea (Celebrex® immediate-release capsules; NDA-020998, 12/31/1998; NDA-021156, 12/23/1999; by Pfizer). The maximum approved oral dose is 400 mg (as a single dose for treatment initiation) with other indication specific dosing (e.g. 100 mg twice daily, 200 mg once daily, 200 mg twice daily in adults). It is recommended to use at lowest effective dose for the shortest duration. Moreover, reduced dosing is suggested in subjects with moderate hepatic impairment or poor metabolizers of CYP2C9.The Sponsor relies on the clinical pharmacology data available from listed drug (Celebrex capsules; NDA-020998).

The product is formulated (b) (4) oral solution (DFN-15; 25 mg/mL) of celecoxib. The sponsor claims that the solubilization of celecoxib in gastrointestinal fluids using their self-micro-emulsifying drug delivery system overcomes the solubility limited absorption, improving the rate and relative bioavailability of celecoxib compared to oral immediate-release capsule formulation. For the treatment of migraine, the proposed dose is 120 mg to be given orally using (b) (4) oral solution.

During the development, the sponsor conducted a randomized, open-label, balanced, 3-treatment, 3-period, 6-sequence, cross-over study assessing comparative bioavailability between to-be marketed formulation (DFN-15, 25 mg/mL; 120 mg oral solution) and listed drug (Celebrex; Celecoxib 400 mg capsule) in healthy subjects.

The peak concentrations of 1811 ± 729 ng/mL were observed following single oral dose of listed drug (Celebrex; Celecoxib 400 mg capsule) under fed condition. While, the peak concentrations of 514.4 ± 174 ng/mL were observed following single oral dose of test product (DFN-15, 25 mg/mL; 120 mg oral solution) under fed condition. The text product exhibited negative food effect with lower Cmax (993 ± 218 vs. 514.4 ± 174 ng/mL) under fed condition.

The to-be-marketed formulation of DFN-15 was compared with the LD, Celebrex capsules 400 mg, in a comparative bioavailability (bridging) study in 24 healthy subjects (DFN-15-CD- 008). A single dose of DFN-15 120 mg, administered under fasting and fed conditions, was compared with Celebrex (celecoxib) capsules 400 mg, administered under fed condition. The median time to maximum concentration (Tmax) of celecoxib from DFN-15 under the fasting state was reached at 1 hour post dose, earlier than that seen with Celebrex capsules (3.5 hours) under the fed state. The mean maximum concentration (Cmax) and area under the concentration-time curve (AUC0-∞) of celecoxib derived from DFN-15 intake (fasting) were approximately 43% and 28% lower, respectively, than those from Celebrex 400 mg capsules. With high-fat food, the Tmax from DFN-15 was 3 hours post dose, with about a 50% lower Cmax and no change in AUC compared to DFN-15 given in fasting state.

Therefore, DFN-15 at the single dose of 120 mg, under both fasting and fed conditions, provides lower exposure to celecoxib than the maximum single dose approved for the LD of 400 mg, under fed condition.

The sponsor claims lack of effects of celecoxib on QT prolongation cardiovascular system during routine safety monitoring in their clinical studies. These studies were not designed to characterize risk of QT prolongation associated with celecoxib administration.

In the two Phase 3 clinical trials of DFN-15 in migraine patients (DFN-15-CD-006 and DFN-15-CD-007), a total of 578 and 571 subjects, respectively, received at least one dose of the study drug (DFN-15 or placebo). The subjects were evaluated by 12-lead electrocardiogram (ECG) during these studies at screening, baseline (pre-randomization) and at the end of each treatment period.

In Study DFN-15-CD-006, 2 subjects had ECG abnormalities; both subjects received placebo, and neither events were considered related to the study treatment. No ECG abnormalities associated with DFN-15 were reported in study DFN-15-CD-007.

Overall, there was no evidence of QT interval prolongation associated with DFN-15 use.

Celecoxib is known to be associated with an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. The sponsor conducted literature search and summarized the effects of celecoxib on QT prolongation (see below). The sponsor claims that no new cardiac safety issues were identified in the published literature during reporting period.

As with all NSAIDs, celecoxib is associated with an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with increased duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (Celebrex prescribing information).

A literature search on PubMed was conducted to identify articles published through 30 Nov 2018 that may add to the current labeling regarding potential effects of celecoxib on QT interval.

Search strategy:

- Searched for all records in which both: o celecoxib appeared in the title, identifier, subject, or trade name fields; and o QT appeared in the abstract, title, identifier, or subject fields; or electrocardiogram, electrocardiograph, ECG, or EKG appeared in the abstract, title, identifier, or subject fields.
- Search results that are not relevant were removed.

The searches identified clinical and nonclinical studies. All the abstracts were reviewed for those that might contain clinical or nonclinical information relevant to the safety (ECG changes and QT prolongation in particular) of celecoxib. Three relevant studies were identified and are summarized below.

- In a rodent study, an amorphous celecoxib formulation was associated with QT interval prolongation at a very high dose of 500 mg/kg (Sharma et al, 2009).
- In an in vitro study, celecoxib inhibited the hERG, SCN5A, KCNQ1 and KCNQ1/MinK channels expressed in HEK-293 cells and the KCND3/KChiP2 channels expressed in CHO cells (Frolov et al, 2011). The implication of the findings in vivo has not been explored.

- In a study of healthy adults and inflammatory arthritis patients with or without celecoxib use for more than 2 months, the P-wave duration was longer in inflammatory arthritis patients taking celecoxib compared with healthy adults (p=0.049) and arthritis patients not on celecoxib (p=0.036) (Pizzuto et al, 2014). The mean P-wave duration (standard error of the mean) in the arthritis patients taking celecoxib was 133.1 (2.7) milliseconds (ms), 125.3 (1.6) ms in the healthy adults, and 124.0 (2.9) ms in the arthritis patients without celecoxib use.

In summary, no new cardiac safety issues were identified in the published literature during the reporting period that warrants revision of the current labeling for celecoxib.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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/s/

GIRISH K BENDE
09/30/2019 12:35:57 PM

CHRISTINE E GARNETT
09/30/2019 12:44:57 PM

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: 9/12/2019

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: **Decline to conduct an on-site inspection**

RE: NDA 212157

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4). The inspection was conducted under the following submission: BLA (b) (4).

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

TING WANG
09/12/2019 09:01:59 AM

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:	April 28, 2020
To:	Harold Sano, PharmD, MBA, BCOP, CIP Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	ELYXYB (celecoxib)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 212157
Applicant:	Dr. Reddy's Laboratories, Ltd.

1 INTRODUCTION

On July 5, 2019, Dr. Reddy's Laboratories, Ltd. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 212157 for ELYXYB (celecoxib). Celecoxib is approved as a nonsteroidal anti-inflammatory drug indicated for: osteoarthritis, rheumatoid arthritis in patients 2 years and older, ankylosing spondylitis, acute pain and primary dysmenorrhea. Dr. Reddy's Laboratories, Ltd. has developed a new formulation, celecoxib oral solution. The proposed indication is for the acute treatment of migraine with or without aura in adults.

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 II (DN2) on July 23, 2019 and July 19, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ELYXYB (celecoxib) oral solution.

2 MATERIAL REVIEWED

- Draft ELYXYB (celecoxib) MG and IFU received on July 5, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 14, 2020 and April 21, 2020, respectively.
- Draft ELYXYB (celecoxib) Prescribing Information (PI) received on July 5, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 14, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, 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 MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are 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 MG and IFU.

Please let us know if you have any questions.

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/s/

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04/28/2020 11:02:56 AM

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MARCIA B WILLIAMS
04/28/2020 11:12:13 AM

LASHAWN M GRIFFITHS
04/28/2020 11:46:45 AM

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

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

Memorandum

Date: April 27, 2020

To: Viveca Livezey, M.D.
Division of Neurology II (DN II)

Sano Harold, Regulatory Project Manager

Tracy Peters, Associate Director for Labeling, DN I

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

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELYXYB (celecoxib) oral solution

NDA: 212157

In response to the DN II consult request dated July 19, 2019, OPDP has reviewed the proposed product labeling (PI),Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ELYXYB (celecoxib) oral solution.

PI, Medication Guide, IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN II (Harold Sano) on April 14, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU 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 March 13, 2020, and April 20, 2020, 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.

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DHARA SHAH
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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:	April 27, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 212157
Product Name and Strength:	Elyxyb (celecoxib) Oral Solution 120 mg/4.8 mL (25 mg/mL)
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
OSE RCM #:	2019-1469-3
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton and Instructions for Use (IFU) labeling received on April 24, 2020 for Elyxyb. The Division of Neurology 2 (DN2) requested that we review the revised labeling for Elyxyb (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Weitzman B. Label and Labeling Review for Elyxyb (NDA 212157). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 22. RCM No.: 2019-1469-2.

APPENDIX A. IMAGES OF LABELING RECEIVED ON APRIL 24, 2020

- Commercial carton labeling
- Professional sample carton labeling
- Instructions for use (no image)

Available in EDR via: \\cdsesub1\evsprod\nda212157\0027\m1\us\114-labeling\draft-labeling\draft-labeling-text\ifu.docx

Excerpt from April 24, 2020 proposed IFU submission:

(b) (4)

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BEVERLY WEITZMAN
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BRIANA B RIDER
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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:	April 22, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 212157
Product Name and Strength:	Elyxyb (celecoxib) Oral Solution 120 mg/4.8 mL (25 mg/mL)
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
OSE RCM #:	2019-1469-2
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

On April 20, 2020, the Applicant submitted revised carton and Instructions for Use (IFU) labeling and responses to recommendations that we made during a previous label and labeling review[a] and information request[b] for Elyxyb (celecoxib) Oral Solution. The Division of Neurology 2 (DN2) requested that we review the responses and revised labels and labeling to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The revised Instructions for Use (IFU) and carton labeling (See Appendix B) are unacceptable from a medication error perspective for the following reasons:

- The carton labeling contains the term "(b) (4)". The term "(b) (4)" may be misinterpreted to mean the (b) (4)

[a] Weitzman B. Label and Labeling Review for Elyxyb (NDA 212157). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 02. RCM No.: 2019-1469-1.
[b] Available in DARRTS via:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80558a24&_afrRedirect=6954622463585280

- The bottle of water depicted in the IFU Instructions-1 (120 mg dose) step 5 and Instructions-2 (60 mg dose) step 6 resembles the bottle of Elyxyb with regard to the shape and color and can be improved to minimize the risk of confusion.
- The IFU Instructions-2 (60 mg dose) step 2 provides instruction to withdraw 2.4 mL of the drug product using an oral dosing syringe. However, this step lacks sufficient details for users to perform this step safely and effectively.

3. RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES LIMITED

We recommend the following be implemented prior to approval of this NDA 212157:

A. Carton Labeling:
   1. The carton labeling contains the term "(b) (4)". The term "(b) (4)" may be misinterpreted to mean the (b) (4). Delete the term "(b) (4)" from the carton labeling, and wherever else it appears in the labeling.

B. Instructions for use (IFU):
   1. The bottle of water depicted in the IFU Instructions-1 (120 mg dose) step 5 and Instructions-2 (60 mg dose) step 6 resembles the bottle of Elyxyb with regard to the shape and color and can be improved to minimize the risk of confusion. Revise the water bottle image to better distinguish it from the bottle of Elyxyb. For example, consider including an image of a glass of water, as opposed to a bottle.
   2. The IFU Instructions-2 (60 mg dose) step 2 provides instruction to withdraw 2.4 mL of the drug product using an oral dosing syringe obtained from the pharmacy. However, this step lacks sufficient details for users to perform this step safely and effectively. Revise the IFU to provide clear directions on how to withdraw and measure 2.4 mL of the drug product. For example, consider whether an oral dosing syringe would fit in the bottle opening, or whether the oral solution will need to be poured into something else (e.g., medicine cup) and then withdrawn using the oral dosing syringe.

APPENDIX A: APPLICANT'S RESPONSE TO THE AGENCY'S APRIL 16, 2020 INFORMATION REQUEST COMMENTS RECEVIED ON APRIL 20, 2020.
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Excerpt from submission:

Comment 1:

We refer to your NDA 212157 received on July 5, 2019, for Elyxyb (celecoxib) oral solution and to the revised labels and labeling received on April 8, 2020.

(b) (4)

(b) (4) **we recommend you consider whether accurate dosing can be accomplished by labeling your product for use with an oral dosing syringe that can be obtained from the pharmacy, until a packaging configuration specific for this patient population (i.e., 60 mg/2.4 mL bottle) is developed.**

Dr. Reddy's Response:

Dr. Reddy's acknowledges Agency's comment and agrees with the recommendation to use an oral dosing syringe obtained from the pharmacy for dosing of patient population that requires 50% dose reduction (60 mg/2.4 mL) until a packaging configuration specific for this patient population (60 mg/2.4 mL bottle) is developed.

The commercial and physician sample carton labels (submitted in Sequence 0022 on April 8, 2020) have been updated (b) (4)
We have also revised the Instructions for Use (IFU) (b) (4)
(b) (4) for using oral dosing syringe that can be obtained from the pharmacy for patient population requiring 50% dose reduction. The revised commercial and physician sample carton labels and Instructions for Use are included in this submission.

APPENDIX B. IMAGES OF LABELS AND LABELING RECEIVED ON APRIL 20, 2020

- Commercial carton labeling
- Professional sample carton labeling
- Instructions for use (no image)

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BEVERLY WEITZMAN
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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:	April 2, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 212157
Product Name and Strength:	Elyxyb (celecoxib) Oral Solution, 120 mg/4.8 mL (25 mg/mL)
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
OSE RCM #:	2019-1469-1
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

On March 13, 2020, the Applicant submitted revised labels and labeling in response to recommendations that we made during a previous label and labeling review[a] for Elyxyb (celecoxib) Oral Solution. The Division of Neurology 2 (DN2) requested that we review the revised labels and labeling (See Appendix A) to determine if they acceptable from a medication error perspective.

2 CONCLUSION

The revised container labels (commercial and physician sample) are acceptable from a medication error perspective. However, the carton labeling (commercial and physician sample) and Instruction for Use (IFU) are unacceptable from a medication error perspective for the following reasons:

- (b) (4)

[a] Weitzman B. Label and Labeling Review for Elyxyb (NDA 212157). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 30. RCM No.: 2019-1469.

- The statement [redacted] (b) (4) " has been added to the carton labeling. However, the dosing for this product is variable. As such, inclusion of this statement may contribute to dosing errors.
- It is unclear whether the bottles are intended for individual dispensing. The carton contains important safety information that may not be available to users if bottles are dispensed individually.
- The image in the IFU suggests holding the bottle upside down for 10 seconds, whereas the instructions to the right of the image state to hold the bottle upside down for [redacted] (b) (4) 10 seconds. The image and instructions do not match, which may lead to confusion regarding how long to hold the bottle upside down.
- A currently presented, there are two sets of instructions included in the IFU based on the prescribed dose (120 mg/4.8 mL or 60 mg/2.4 mL). However, we are concerned that the instructions for the prescribe dose of 60 mg/2.4 mL (i.e., 50% reduction in dose) may be overlooked, which may lead to dosing errors, specifically "overdose" errors in patients that require a 50% dose reduction.

3. RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES LIMITED

We recommend the following be implemented prior to approval of this NDA 212157:

A. General

1. [redacted] (b) (4)

B. Carton labeling (commercial and physician sample):

1. The statement [redacted] (b) (4) " has been added to the carton labeling. However, the dosing for this product is variable. As such, inclusion of this statement may contribute to dosing errors. We recommend deleting the [redacted] (b) (4) from the carton labeling. Additionally, we recommend you add a warning prominently to the principal display panel of the carton labeling, such as: "Check the dose your healthcare provider has prescribed", or similar.
2. It is unclear whether the bottles are intended for individual dispensing. The carton contains important safety information that may not be available to users if bottles are dispensed individually. Clarify whether bottles are intended for individual dispensing or whether they should be dispensed in the sealed carton. If the later, consider revising the carton labeling to state "Dispense in this sealed carton" on the principal display panel, or address this concern by other means.

C. Instructions for use (IFU):

1. The image in the IFU suggests holding the bottle upside down for 10 seconds, whereas the instructions to the right of the image state to hold the bottle upside down for (b) (4) 10 seconds. The image and instructions do not match, which may lead to confusion regarding how long to hold the bottle upside down. Revise the instructions and/or the image so that both convey the same information.
2. The IFU contain two sets of instructions based on the prescribed dose (that is, 120 mg/4.8 mL or 60 mg/2.4 mL). As currently presented, the instructions for the 60 mg/2.4 mL dose may be overlooked, which may lead to dosing errors, specifically "overdose" errors in patients that require a 50% dose reduction. Revise the IFU to ensure that users can identify and follow the instructions applicable to them. For example, add instruction for users to check the dose the healthcare provider has prescribed. If the healthcare provider has prescribed 120 mg of Elyxyb, do x. If the healthcare provider has prescribed 60 mg of Elyxyb, do y. Or, address this concern by other means.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 13, 2020.

- Commercial carton labeling
- Professional sample carton labeling
- Commercial container label
- Professional sample container label
- Instruction for use (no image)
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BEVERLY WEITZMAN
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04/03/2020 09:26:09 AM

Clinical Inspection Summary

Date	2/20/2020
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Harold Sano, Pharm.D., Regulatory Project Manager Viveca Livezey, M.D., Medical Officer Division of Neurology 2 Office of Neuroscience
NDA #	212157
Applicant	Dr. Reddy's Laboratories Ltd.
Drug	Celecoxib oral solution
NME	No
Proposed Indication	Treatment of (b) (4) migraines with or without aura in adults
Consultation Request Date	10/1/2019
Summary Goal Date	2/28/2020
Priority/Standard Review	Standard
Action Goal Date	5/5/2020
PDUFA Date	5/5/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Blanco, DeAtkine, Lillo, and Tidman were inspected in support of this NDA. The inspections covered Protocols DFN-15-CD-006 and DFN-15-CD-007. Under-reporting of non-serious adverse events and concomitant medications was noted at Dr. Tidman's site for a small percentage of subjects. Otherwise, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Celecoxib oral solution is being developed by Dr. Reddy's Laboratories Limited for the treatment of (b) (4) migraine with or without aura in adults under NDA 212157 (IND 125585) as a 505(b)(2) application. The reference listed drug for this application is Celebrex®, which was originally approved in 1998, is available as an oral capsule formulation, and is approved for the treatment of a number of different pain syndromes but not for the treatment of migraine.

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID). NSAIDS have analgesic, antipyretic, and anti-inflammatory effects that act by inhibition of prostaglandin biosynthesis through isoenzymes cyclooxygenases 1 and 2 (COX-1 and COX-2).

Celecoxib inhibits prostaglandin formation via inhibition of COX-2, which may spare the prostaglandins that are responsible for the maintenance and protection of the gastrointestinal tract (synthesized involving COX-1).

The sponsor submitted two Phase 3 studies, DFN-15-CD-006 and DFN-15-CD-007, to support the efficacy and safety of celecoxib for the treatment of migraine.

Protocol DFN-15-CD-006

Title: "A multicenter, randomized, double-blind, placebo-controlled, efficacy, tolerability, and safety study of DFN-15 [celecoxib] in episodic migraine with or without aura"

Subjects: 631 randomized

Sites: 41 sites in the United States

Study Initiation and Completion Dates: 12/5/2016 – 10/12/2017

This was a Phase 3, randomized, double-blind, placebo-controlled study with two double-blind treatment periods. Major eligibility criteria were male or female subjects, 18 to 75 years of age; previously diagnosed with at least 12 months medical history of episodic migraine, 2 to 8 migraine attacks (with or without aura) per month, ≤14 headache days per month, and with 48 hours of headache-free time between migraine attacks.

The study design consisted of three periods:

Screening Period: up to three weeks to determine subject eligibility

First Double-Blind (DB1) Period: up to 4 weeks

Subjects were randomized (1:1) to:

- Celecoxib 25 mg/mL; 4.8 mL (120 mg) or
- Placebo 4.8 mL

A migraine attack was treated with study drug as soon as, and no more than 1 hour, after experiencing moderate to severe migraine pain.

Second Double-Bind (DB2) Period: up to 4 weeks

Subjects returned to the study site within 2 to 7 days of the first treatment (DB1).
Subjects were re-randomized (1:1) to:

- Celecoxib 25 mg/mL; 4.8 mL (120 mg) or
- Placebo 4.8 mL

A migraine attack of any severity was treated with study drug.
Subjects then returned to the study site within 2 to 7 days of the second treatment for the final visit.

During the treatment periods, data regarding the study drug effect and the associated impact on migraine pain, symptoms, functional disability, and subjects' satisfaction with

treatment were collected in real-time in an electronic diary (eDiary). Subjects were to rate migraine symptoms (pain, most bothersome symptom) at the following timepoints: predose, and postdose at 15, 30, and 45 minutes, and 1, 1.5, 2, 4, and 24 hours. Subjects could take rescue pain medications after the 2-hour postdose timepoint and this information was to be entered into the eDiary.

The *co-primary efficacy endpoints* were the following and applied only to the DB1 study period:

- The proportion of subjects who are pain-free 2 hours post-dose compared between celecoxib and placebo in the DB1 period (defined as a reduction from pre-dose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]).
- The proportion of subjects who are free from their Screening most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours post-dose compared between celecoxib and placebo in the DB1 period.

Protocol DFN-15-CD-007

Title: "A multicenter, randomized, double-blind, placebo-controlled, efficacy, tolerability, and safety study of DFN-15 [celecoxib] in episodic migraine with or without aura"

Subjects: 622 randomized

Sites: 44 sites in the United States

Study Initiation and Completion Dates: 12/13/2016 – 10/6/2017

The study design was identical to DFN-15-CD-006.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, site efficacy, high placebo response (site 609), numbers of enrolled subjects, and prior inspectional history.

III. RESULTS

1. **Antonio Blanco, M.D.**
   Site #603
   11440 North Kendall Drive, Suite 308
   Miami, FL 33176
   Inspection Dates: 12/2/2019 – 12/5/2019

   At this site for Protocol DFN-15-CD-006, 32 subjects were screened, 29 were enrolled and randomized, and 23 subjects completed the study. Three subjects were discontinued from the study since they did not have migraine of sufficient severity in DB1 (and therefore did not take

study medication). Three additional subjects discontinued the study due to withdrawal of consent (n=2) and protocol violation (not specified) (n=1).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine pain and most bothersome symptom).

The clinical site printed out the eDiary data at each scheduled visit and placed it in the subjects' study binder. Migraine data from these printouts were used to verify against sponsor line listings; no discrepancies were identified. There was no evidence of underreporting of adverse events, and no SAEs occurred at this site.

2. **David DeAtkine, M.D.**
Site #609
2660 10th Avenue South
Building 1, Suite 735
Birmingham, AL 35205
Inspection Dates: 1/13/2020 – 1/16/2020

At this site for Protocol DFN-15-CD-006, 40 subjects were screened, 28 were enrolled and randomized, and 25 subjects completed the study. Two subjects were discontinued from the study since they did not have migraine of sufficient severity in DB1 (and therefore did not take study medication). One additional subject was discontinued due to a protocol violation (not specified).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine pain and most bothersome symptom).

The clinical site printed out the eDiary data at each scheduled visit and placed it in the subjects' study binder. Migraine data from these printouts were used to verify against sponsor line listings; no discrepancies were identified. There was no evidence of underreporting of adverse events, and no SAEs occurred at this site.

3. **Joseph Lillo, M.D**
Site #727
4520 East Indian School Road
Phoenix, AZ 85018
Inspection Dates: 12/2/2019 – 12/9/2019

At this site for Protocol DFN-15-CD-007, 60 subjects were screened, 29 were enrolled and randomized, and 23 subjects completed the study. Three subjects were discontinued from the study since they did not have migraine of sufficient severity in DB1 (and therefore did not take study medication). Three additional subjects were discontinued due to withdrawal of consent (n=1) and protocol violation (use of prohibited medication) (n=2).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine pain and most bothersome symptom).

The clinical site printed out the eDiary data at each scheduled visit and placed it in the subjects' study binder. Migraine data from these printouts were used to verify against sponsor line listings; no discrepancies were identified. There was no evidence of underreporting of adverse events, and no SAEs occurred at this site.

4. **Raymond Tidman, M.D**
Site #740
101 Riverstone Vista, Suite 201
Blue Ridge, GA 30513
Inspection Dates: 12/2/2019 – 12/4/2019

At this site for Protocol DFN-15-CD-007, 18 subjects were screened, 12 were enrolled and randomized, and 9 subjects completed the study. Two subjects were discontinued from the study since they did not have migraine of sufficient severity in DB1 (and therefore did not take study medication), and one subject was discontinued after randomization due to a protocol violation (use of prohibited medication).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine pain and most bothersome symptom).

The clinical site printed out the eDiary data at each scheduled visit and placed it in the

subjects' study binder. Migraine data from these printouts were used to verify against sponsor line listings; no discrepancies were identified.

No SAEs occurred at this site. The inspection noted an under-reporting of non-serious adverse events and of concomitant medications for two of 12 (16.7%) enrolled subjects:

- Subject (b) (6) was randomized to placebo on 1/12/17 (dosed on 1/22/17), re-randomized to celecoxib on 1/24/17 (dosed on 2/16/17), and completed the study on 2/23/17. This subject had an unscheduled visit on 1/26/2017 due to bronchitis and acute respiratory infection. Neither of these were listed as adverse events. Medical progress notes indicate that the subject was to be treated with an albuterol inhaler and benzonatate. These medications are not listed as concomitant medications; however, it is not known whether the subject obtained these medications and administered them. However, during this visit, a dexamethasone injection was administered, which was not reported as a concomitant medication.

- Subject (b) (6) was randomized to celecoxib on 2/23/17 (dosed on 3/2/17), re-randomized to placebo on 3/6/17 (dosed on 3/29/17), and completed the study on 4/5/2017. This subject had an unscheduled visit on 3/3/17 for worsening lower back pain, worsening of neck pain, and weight gain. Diagnosis included cervical disc disorder at C5-C6 with radiculopathy and low back pain. Sponsor line listings for this subject's medical history include musculoskeletal and connective tissue disorders/arthritis (back) but do not indicate history of arthritis in the neck. Even the pre-existing symptoms should have been reported as adverse events since they had worsened in severity. At this visit, the subject's dose of venlafaxine was decreased from 150 mg daily to 75 mg daily due to weight gain; this change in dose was not reported in the concomitant medication log.

  On 3/20/17, this subject phoned to complain of continued lower back pain and requested a prescription for tramadol since the ibuprofen was not alleviating her pain. A prescription for tramadol (one QID, #30) was phoned to the pharmacy. Sponsor line listings for this subject do not include tramadol as a concomitant medication. In addition, the line listings do not include ibuprofen use for back pain. Ibuprofen use as a rescue medication for migraine pain would be recorded in the eDiary by the subject but not if used for another indication.

Reviewer comments: The clinical investigator should have reported the adverse events occurring in these subjects. However, it is unlikely that the under-reporting of adverse events in these two subjects would impact overall safety analyses for this application. The described adverse events are included in the approved label for the reference listed drug, Celebrex®.

The under-reporting of concomitant medications, especially for Subject (b) (6), could impact the subjects' efficacy data. It is not known how often the subject took ibuprofen for back pain during the study or when the subject administered tramadol for back pain. In addition, although venlafaxine was prescribed for this subject for depression, it has some efficacy for migraine prophylaxis. Therefore, a reduction in venlafaxine dose may impact migraine pain,

both directly and indirectly (i.e., headache pain can be a symptom of venlafaxine withdrawal when doses are reduced). However, the greatest impact for this concomitant medication use would have occurred in DB2 and not DB1, the latter being the time point for the primary efficacy endpoint.

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LABEL AND LABELING REVIEW
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)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 30, 2020
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212157
Product Name and Strength:	Elyxyb (celecoxib) Oral Solution, 120 mg/4.8 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Dr. Reddy's Laboratories Limited
FDA Received Dates:	July, 5, 2019 (Physician sample and commercial carton labeling and physician sample container label) September 10, 2019 (Commercial container Label) October 4, 2019 (Revised Prescribing Information) December 13, 2019 (Instructions for Use)
OSE RCM #:	2019-1469
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for Elyxyb (celecoxib) oral solution, the Division of Neurology Products (DNP) requested that we review the proposed prescribing information (PI), medication guide (MG), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other – Information Request	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 ASSESSMENT

We identified that the proposed packaging configuration (i.e., 10 mL unit dose glass bottles containing 120 mg/4.8 mL) is not optimized for all the recommended dosages in the Dosage and Administration section of the Prescribing Information (PI). Specifically, for a dose modification to a dose of 60 mg, a 50% reduction.

We discussed with the Medical Officer the potential negative clinical consequences of patients who require a 50% reduction in dose (i.e., patients with hepatic impairment and poor metabolizers of CYP2C9 substrates) unintentionally receiving a full dose (i.e., 2-fold overdose). Per the Medical Officer, in patients with liver disease, some potential consequences of higher dosages than intended could be: cholestatic, hepatocellular or mixed liver injury- all of which can be severe; possible decreasing platelet aggregation (leading to coagulopathy being compounded) and also potentially affecting kidney function (since cirrhotic patients with portal hypertension are dependent on prostaglandins to counteract the Renin-angiotensin-aldosterone system, maintain glomerular filtration rate and prevent sodium retention). In CYP2C9 poor metabolizers, potential clinical consequences could be an exacerbation of all potential adverse effects (including gastrointestinal/cardiac and renal toxicities) since celecoxib will take longer to be metabolized.

We recommend that for future development, the Sponsor consider developing a packaging configuration for patients who require a 50% dose reduction, to minimize the risk of 2-fold overdoses in this population.

We note the labels and labeling of the proposed packaging configuration can be improved to help mitigate the risk of overdose medication errors in patients who require a 50% reduction in dose. We provide recommendations in Table 2 and Table 3 below to address these concerns.

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), medication guide, container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) – General			
1.	(b) (4)		
2.	The product strength is expressed as 25 mg/mL throughout the PI.	The strength expression can be improved to minimize the risk of confusion and/or dosing errors.	We recommend expressing the strength as the total quantity per total volume (i.e., 120 mg/4.8 mL) followed by the amount per mL (i.e., 25 mg/mL) throughout the PI. For example, 120 mg/4.8 mL (25 mg/mL).
Highlights of PI (HPI) and Full PI (FPI) - Dosage and Administration (Section 2)			
3.	The frequency statement "(b) (4) is unclear.	It is unclear whether there is a maximum number of doses permitted over a certain period of time (e.g., 24 hours),	We recommend clarifying if there is a maximum number of doses permitted over a certain period time (e.g., 24 hours), or if

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		or if there is a certain period of time the user should wait before they take the next dose. This may lead to wrong frequency of administration medication errors.	there is a certain period of time users should wait before they take next dose.
FPI – Dosage and Administration (Section 2)			
4.	As currently presented, important dosage and administration information for special populations may be easily overlooked.	Presenting important dosage and administration information to the reader in a continuous format may decrease readability.	To increase readability, consider the use of additional subsections within Section 2: Dosage and Administration. For example, consider organizing information into the following subsections: 2.1 Recommended dose 2.2 Special populations Hepatic impairment Poor Metabolizers 2.3 Administration Instructions
5.	The Dosage and Administration section of the PI (Section 2) lacks information regarding how to appropriately measure and deliver the prescribed dose accurately.	We are concerned that the lack of proper measuring information may lead to dosing errors, specifically "over dose" errors in patients that require a 50% dose reduction.	We recommend the statement "(b) (4) " be revised to read: "(b) (4) An oral dosing syringe is recommended to measure and deliver the prescribed dose accurately. A household teaspoon is not an adequate measuring device."
FPI – Patient Counseling Information (Section 17)			
6.	Important administration instructions are missing.	Can be improved to minimize the risk of medication dosing errors and to ensure the dose is measured and administered accurately.	We recommend adding the following statements to section 17 of the PI: "Instruct patients or caregivers to use an oral dosing syringe to

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		In addition, evidence suggests use of oral syringes may decrease the risk of wrong dose error, particularly when measuring smaller doses (i.e., less than 5 mL).[a]	correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy. Patients should be advised that a household teaspoon is not an accurate measuring device."
Instructions for Use (IFU)			
7.	The image in the IFU suggests to hold the bottle upside down for 10 seconds, whereas the instructions to the right of the image state to hold the bottle upside down for (b) (4) 10 seconds.	The image and instructions do not match, which may lead to confusion on how long to hold the bottle upside down.	Consider revising the instructions and/or the image so that both convey the same information.
8.	The instruction " (b) (4) " lacks clarity.	The instruction " (b) (4) " could be interpreted as discard bottle once bottle is completely empty. Thus, the end user may use the amount of leftover drug for subsequent doses, which may pose risk of deteriorated drug medication errors.	We recommend clarifying when the bottle should be discarded. For example, "Discard unused portion immediately after use. Do not store or reuse leftover Elyxyb oral solution."

Table 3. Identified Issues and Recommendations for Dr. Reddy's Laboratories Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations			
1.	Proposed packaging configuration (10 mL unit dose glass bottles	We are concerned that patients prescribed a 50% dose reduction may consume	We recommend for future development you consider developing a packaging

[a] Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. Pediatrics. 2016; 138(4): e20160357

Table 3. Identified Issues and Recommendations for Dr. Reddy's Laboratories Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	containing 120 mg/4.8 mL) is not appropriate for all recommended dosages; specifically, for a dose modification to a dose of 60 mg (50% dose reduction).	the entire contents of the unit dose bottle resulting in a 2-fold overdose.	configuration for this patient population (e.g., 60 mg/2.4 mL bottle) to help mitigate the risk of overdose medication errors. Additional recommendations are provided below to help mitigate potential for overdose errors.
2.	The proposed labels and labeling lack adequate instructions for users to measure and administer their prescribed dose.	The lack of instruction on how to accurately measure and administer the prescribed dose (i.e., 4.8 mL or 2.4 mL) may result in wrong dose medication errors.	If users need to follow specific instructions to accurately measure and administer their prescribed dose, revise the labels and labeling (e.g., 'Patient Counseling Information' section of the PI, Instructions for Use, carton labeling) to provide such instructions.
General Recommendations (Container Label and Carton Labeling, Commercial and Physician Sample)			
3.	The proprietary name is written in all-capital letters.	Words written in all-capital letters are less legible than words written in mixed case letters.[b]	Consider capitalizing only the first letter in the proprietary name (i.e., Elyxyb).
4.	The package type statements (b) (4) " are misleading.	The term (b) (4) " may be misinterpreted to mean the entire contents of the bottle equals one dose, which poses risk of overdose errors. (b) (4)	To minimize the risk of overdose medication dosing errors, remove the statements " (b) (4) "

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Dr. Reddy's Laboratories Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		specified dose, which poses risk of overdose errors.	
5.	The usual dosage statement can be improved.	To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information.	Revise the statement, (b) (4) to read: "Recommended Dosage: See prescribing information."
6.	There is a warning that contains a negative statement (i.e., (b) (4)	Postmarketing reports suggest negative statements may be misinterpreted as an affirmative action if the word "not" is overlooked. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf).	Delete the negative warning statement "(b) (4) as the appropriate storage information (store at room temperature) is already provided in affirmative language.
Container Label (Commercial and Physician Sample)			
7.	The net quantity statement is missing from the principal display panel (PDP).	The net quantity statement is required to appear on the container label per 21 CFR 201.51.	Add the net quantity statement (4.8 mL) to the PDP in accordance with Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf). Ensure that the net quantity statement is located away from the strength statement, such as to the bottom of the PDP, to minimize the risk for confusion.
Carton Labeling (Commercial & Physician Sample)			

Table 3. Identified Issues and Recommendations for Dr. Reddy's Laboratories Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
8.	The instruction (b) (4) lacks clarity.	The instruction "(b) (4)" could be interpreted as discard bottle once bottle is completely empty. Thus, the end user may use the amount of leftover drug for subsequent doses, which may pose risk of deteriorated drug medication errors.	Clarify when the bottle should be discarded. For example, "Discard unused portion immediately after use. Do not store or reuse leftover Elyxyb oral solution." Additionally, we recommend adding a similar statement to the PDP of the container label.
9.	The product has a Medication Guide; however, the required Medication Guide statement is omitted from the principal display panel (PDP).	Per 21 CFR 208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided.	Revise the PDP to include the statement "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" or a similar statement, in accordance with 21 CFR 208.24(d).
10.	On the side panel, the statement of package contents can be improved.	Can be improved to clarify the strength of each bottle.	Consider revising the first bullet point to read: "Nine (9) glass bottles. Each bottle contains 120 mg/4.8 mL (25 mg/mL)" for the commercial carton labeling and "One (1) glass bottle containing 120 mg/4.8 mL (25 mg/mL)" for the physician sample carton labeling.
Instructions for Use (IFU)			
11.	The Instructions for Use do not provide instructions for patients who require a 50% reduction in dose.	As currently proposed, the Instructions For Use pose risk of patients who require a 50% reduction in dose drinking the entire bottle, which would result in a two-fold overdose.	Revise the Instructions for Use to address our concerns regarding the risk of two-fold overdose administration errors in patients who require a 50% reduction in dose.

5 CONCLUSION

Our evaluation of the proposed Elyxyb (celecoxib) oral solution prescribing information (PI), medication guide, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Dr. Reddy's Laboratories Limited so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Elyxyb (celecoxib) oral solution (celecoxib), that Dr. Reddy's Laboratories Limited submitted on July 5, 2019, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Elyxyb (celecoxib) oral solution

Product Name	Celebrex (020998)	Elyxyb (celecoxib) oral solution
Initial Approval Date	12/31/1998	N/A
Active Ingredient	celecoxib	celecoxib
Indication	Osteoarthritis (OA) Rheumatoid Arthritis (RA) Juvenile Rheumatoid Arthritis in patients 2 years and older Ankylosing Spondylitis (AS) Acute Pain (AP) Primary Dysmenorrhea (PD)	For the acute treatment of migraine with or without aura in adults
Route of Administration	Oral	Oral
Dosage Form	Capsule	Solution
Strength	50 mg, 100 mg, 200 mg and 400 mg	120 mg/4.8 mL (25 mg/mL)
Dose and Frequency	Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals OA: 200 mg once daily or 100 mg twice daily RA: 100 mg to 200 mg twice daily JRA: 50 mg twice daily in patients 10 kg to 25 kg. 100 mg twice daily in patients more than 25 kg AS: 200 mg once daily single dose or 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On	120 mg/4.8 mL once daily during a migraine attack. Dose reduction: 60 mg/2.4 mL for patients with moderate hepatic impairment and poor metabolizers of CYP2C9 substrates.

	subsequent days, 200 mg twice daily as needed Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers.	
How Supplied	50 mg capsules; bottles of 60 100 mg capsules; bottles of 100, 500 and carton of 100 unit dose 200 mg capsules; bottles of 100, 500, carton of 100 unit dose	(b) (4) single dose, disposable glass bottle with CR cap in a carton that contains nine single dose, (b) (4) bottles.
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.
Container Closure	60 count: HDPE bottle with 28 mm CRC; 100 count: HDPE bottles with 38 mm plastic CT cap; 500 count: HDPE bottle with 43 mm Plastic CT; Blisters: PVC w/push-thru paper foil.	10 mL amber glass bottle with 20 mm child resistant closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 1, 2019 we searched for previous DMEPA reviews relevant to this current review using the term, celecoxib. Our search did not identify any previous label and labeling reviews relevant to this review.

APPENDIX E. INFORMATION REQUEST

E.1 Information Request

During our review of the labels and labeling we identified that the proposed packaging configuration may not be appropriate for all the recommended dosages in the Dosage and Administration (D&A) section of the prescribing Information (PI); specifically, for a dose modification to a dose of 60 mg, a 50% reduction. On August 27, 2019, we sent an Information Request to Dr. Reddy to describe how patients who require a 50% dose reduction will achieve their dose. We also requested the Sponsor submit intend-to-market samples to assist with our review.

IR available in DARRTS via:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80510f3b&_afrRedirect=1959756709094300

E.2 Response

The Sponsor responded to DMEPA's IR on September 10, 2019. In their response, Dr Reddy proposed to add the following language to Section 2 (D&A) of the PI: (b) (4) [redacted] ."

Response available in EDR via: \\cdsesub1\evsprod\nda212157\0003\m1\us\111-information-amendment\multiple-module-information-amendments\1114-multi-module-ammendment.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Elyxyb (celecoxib) oral solution labels and labeling submitted by Dr. Reddy's Laboratories Limited.

- Container label received on September 10, 2019
- Carton labeling received on July 5, 2019
- Professional Sample Container received on July 5, 2019
- Professional Sample Carton Labeling received on July 5, 2019
- Medication Guide (Image not shown) received on October 4, 2019
- Instructions for Use (Image not shown) received on December 13, 2019

  Refer to link in EDR for Instructions for Use:

  \\cdsesub1\evsprod\nda212157\0012\m1\us\114-labeling\draft-labeling\draft-labeling-text\ifu.pdf
- Prescribing Information (Image not shown) received on October 4, 2019

  Refer to link in EDR for Prescribing Information:

  \\cdsesub1\evsprod\nda212157\0007\m1\us\114-labeling\draft-labeling\draft-labeling-text\proposed-pi-clean.pdf

F.2 Label and Labeling Images

Container label (Physician Sample)

(b) (4)

[redacted]

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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: January 23, 2020

TO: Nicholas Kozauer, M.D.
Division Director (Acting)
Division of Neurology II (DN II)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Routine inspection of Celerion, Inc., Lincoln, NE.

Inspection Summary

OSIS arranged an inspection of the clinical portion of **Study DFN-15-CD-008** (Celecoxib oral solution, NDA 212157) conducted by Celerion, Inc., Lincoln, NE.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

Recommendation

After reviewing the inspectional findings, I conclude the clinical data from the audited study are reliable to support a regulatory decision.

Inspected Study

NDA 212157

Study Number: DFN-15-CD-008

Study Title: "An open-label, three-way, randomized, single dose crossover study comparing bioavailability of DFN-15 (celecoxib) oral solution (25 mg/mL) 120 mg of Dr. Reddy's Laboratories Limited, India under fasting

conditions versus Celebrex® (celecoxib) 400 mg capsules of G.D. Searle LLC under fed conditions and to determine food-effect of DFN-15 in healthy adult subjects”

Dates of conduct: June 9 – August 22, 2017

Clinical site: Celerion, Inc.
621 Rose Street
Lincoln, NE 68502

ORA Investigator Jonathan R. Campos (OBIMO) inspected Celerion, Lincoln, NE from November 19 - 21, 2019.

The previous BIMO clinical inspection was conducted during March 28 – April 1, 2016 and was classified as NAI. A Form FDA 483 was not issued at the inspection close-out. However, items were discussed with the site’s management regarding protocol adherence and minor documentation discrepancies. During the current inspection, Investigator Campos verified that the listed discussion items have been corrected.

The current inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

Inspectional Findings

At the conclusion of the inspection, Investigator Campos did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, Investigator Campos discussed the following items with the site’s management at the inspection close-out.

Discussion Item #1. The delegation of authority log stated that one of the sub-investigators was not trained on the study protocol but also did not perform any study related tasks. However, the sub-investigator did perform the primary review for the Period 2, 33.75hr post dose ECG results. While this was a task she was qualified to perform as a nurse practitioner, she should have been trained on the protocol.

Site’s Response: At the inspection close-out, the site’s management indicated that they understood the finding but did not commit to making corrections.

OSIS Evaluation: Although it was not the best practice for the sub-investigator to perform the primary review for the Period 2, 33.75hr post dose ECG results without being trained on the protocol, there was no evidence suggesting that any wrong doing had occurred during the conduct of the audited study. Therefore, this finding has no impact on study data integrity.

Discussion Item #2. The categories listed in the delegation of authority responsibilities (**Attachment 1**) are too wide-reaching and not specific to tasks that would actually be performed.

Site's Response: At the inspection close-out, the site's management indicated that they understood the finding. They also stated that the issue with the delegation of authority categories had already been corrected.

OSIS Evaluation: The EIR lacks details to fully assess the objection; However, the site appears to have followed the study protocol and no issues were identified during the inspection. Therefore, this finding has no impact on study data integrity. Since the site had already corrected the issue, the response is adequate.

Discussion Item #3. The subject should be provided an opportunity to ask questions in private before signing the informed consent during the informed consent process.

Site's Response: At the inspection close-out, the site's management indicated that they understood the finding but did not commit to making corrections.

OSIS Evaluation: Although it would be ideal for the potential subjects to have a one-on-one meeting during the informed consent process, it was not required by the regulations. The site conducted the informed consent in a group setting with opportunities to ask questions prior to signing the consent. The site's practice was compliant with 21 CFR Part 50 and considered acceptable. Therefore, this finding has no impact on study data integrity.

Discussion Item #4. The audit trail of the electronic data capture (EDC) system ClinQuick could be modified by personnel with developer level access. Therefore, Investigator Campos considered the EDC system was not compliant with Part 11 and the site should act to get in compliance.

Site's Response: During the inspection, the site provided a Certificate of Compliance of FDA 21 CFR Part 11 (**Attachment 2**). At the inspection close-out, the site's management indicated that they understood the finding but did not commit to making corrections.

OSIS Evaluation: Although it was not the best practice for the "developers" to be able to modify the audit trails of the EDC system, there was no evidence suggesting that any wrong doing had occurred during the conduct of the audited study. Therefore, this finding has no impact on study data integrity.

Additionally, the site appears to have complied with 21 CFR Part 11.10(k) by giving developer level access to developers, and not to personnel who operated the ECD system. Thus, the Certificate of Compliance provided by the site is acceptable.

Conclusion

After reviewing the inspectional findings, I conclude the clinical data from **Study DFN-15-CD-008** (NDA 212157) are reliable.

Based on the inspectional findings, clinical data from studies of similar design conducted by Celerion between the previous inspection (April 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

Yiyue Zhang, Ph.D.
Staff Fellow

Final Classification

Clinical Site

NAI - Celerion, Inc., Lincoln, NE (FEI#: 1915582)

Attachments:

Attachment 1. Delegation of Authority Categories
Attachment 2. Part 11 Certification

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Zhang

OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au
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ORA/OMPTO/OBIMO/DBIMOII/Campos

Draft: YZ 01/21/2020, 01/23/2020
Edit: RCA 1/22/2020, 1/23/2020; AD 01/22/2020, 01/23/2020

ECMS: Cabinets/CDER OTS/Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Celerion, Lincoln, NE

OSIS File#: BE 8687
FACTS: 11956308

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