

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212157Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## RECOMMENDATION: Approval

### NDA 212157 Review #1

<b>Drug Product Name</b>	ELYXYB (celecoxib) oral solution
<b>Dosage Form</b>	Solution
<b>Strength</b>	120 mg/4.8 mL (25 mg/mL)
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Dr. Reddy's Laboratories Limited
<b>US agent, if applicable</b>	Dr. Reddy's Laboratories, Inc.

#### QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
<b>Drug Substance</b>	Rajan Pragani	Suong (Su) Tran
<b>Drug Product</b>	Dan Berger	David Claffey
<b>Manufacturing</b>	Qin (Stefanie) Liang	Tianhong Tim Zhou
<b>Microbiology</b>	Samata Tiwari	Neal Sweeney
<b>Biopharmaceutics</b>	N/A	N/A
<b>Regulatory Business Process Manager</b>	Dahlia Walters/Kelly Ballard	
<b>Application Technical Lead</b>	Martha Heimann	
<b>Laboratory (OTR)</b>	N/A	N/A
<b>Environmental</b>	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-001, Original NDA	7/5/2019	All
SD-006, Response to IR	9/20/2019	Product
SD-008, Response to IR	10/4/2019	Manufacturing
SD-011, Response to IR	11/27/2019	Product
SD-014, Response to IR	12/23/2019	Manufacturing
SD-017, Response to IR	2/14/2020	Manufacturing

## QUALITY ASSESSMENT DATA SHEET

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	Celecoxib	Adequate <sup>1</sup>	--	
	III	(b) (4)	(b) (4)	N/A <sup>2</sup>	--	
	III	(b) (4)	(b) (4)	N/A <sup>2</sup>	--	
	IV	(b) (4)	(b) (4)	N/A <sup>2</sup>	--	
	III	(b) (4)	(b) (4)	N/A <sup>2</sup>	--	

<sup>1</sup> No new information submitted after previous Adequate review.

<sup>2</sup> Adequate information provided in NDA.

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

Document	Application Number	Description
IND	125585	Development of celecoxib oral solution for treatment of migraine.
NDA	20998	Celebrex (celecoxib capsules) is cross-referenced under 505(b)(2) to support safety of celecoxib.

### 2. CONSULTS

None

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 212157 for ELYXYB (celecoxib) oral solution. From a quality perspective, the application provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable for use by the intended patients.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID), that is selective for cyclooxygenase-2 (COX-2). It is approved as Celebrex capsules (and generic equivalents) for management of symptoms of osteoarthritis and rheumatoid arthritis, acute pain in adults, ankylosing spondylitis and primary dysmenorrhea. Celecoxib is not currently approved for treatment of migraine.

The applicant has developed a liquid formulation of celecoxib proposed for treatment of acute migraine. The proposed product is a stable microemulsion, with the appearance of a clear slightly viscous solution. The formulation contains 25 mg/mL celecoxib, (b) (4) glycerin, (b) (4) water, (b) (4) flavoring agents and (b) (4). The product will be packaged in single-dose amber glass bottles containing 4.8 mL of solution (120 mg celecoxib).

Based on the initial risk assessment, Celecoxib Oral Solution is considered a low risk product for all critical attributes except palatability and leachables, which are considered moderate risk.

<b>Proposed indication including intended patient population</b>	Acute treatment of migraine with or without aura in adults
<b>Duration of treatment</b>	(b) (4) intermittent
<b>Maximum daily dose</b>	120 mg
<b>Alternative methods of administration</b>	None

### B. Quality Assessment Overview

*Drug Substance:*           **Adequate**

The active pharmaceutical ingredient (API), Celecoxib USP, is a well-characterized, synthetic small molecule that was initially approved in 1998 and is marketed under multiple applications. approved NDAs and ANDAs. The API is manufactured by (b) (4) and information regarding manufacture and control of the API is

incorporated by cross-reference to the manufacturer's DMF (b) (4). Based on multiple previous reviews, the DMF is deemed adequate to support approval of the NDA. Stability data in the DMF support a (b) (4) **retest date for the API.**

The Applicant's acceptance criteria for the drug substance follows the USP monograph for celecoxib, with additional test for residual solvents and two process-specific related substances that are not included in the monograph. In addition to the monograph tests, additional specification tests such as solvent tests are included that adequately control drug substance production. Both impurities are controlled adequately in the API.

*Drug Product:*                    **Adequate**

Celecoxib oral solution contains the active ingredient, celecoxib, solubilized in a stable, nonaqueous microemulsion (b) (4). The product will be marketed in a single strength, 120 mg/4.8 mL (25 mg/mL). All excipients comply with compendial (USP/NF) standards or are generally recognized as safe (GRAS) for use in foods. The solution is packaged in single-dose amber glass bottles with child-resistant HDPE closures (b) (4). The proposed secondary is a 9-count carton with dividers to protect the bottles from cracking or breakage. The suitability of the container materials was established by appropriate testing, including extractables and leachables testing. As the solution is somewhat viscous, the bottles contain an overfill to ensure delivery of the intended dose when the bottle is inverted for (b) (4) 10 seconds.

The proposed regulatory specifications for celecoxib oral solution include tests, including appearance, identity, assay, related substances, preservative content, viscosity, droplet size, and microbiological testing, to ensure product quality and delivery of the intended dose to the patient. Noncompendial tests are adequately described and validated. The stability data from the registration batches support a **24-month shelf life for product stored at USP Controlled Room Temperature.**

*Labeling:*                            **Adequate**

The proposed labeling is deemed adequate from a quality perspective. Minor revisions to the package insert recommended by the reviewer were made as part of labeling negotiations.

*Manufacturing:*                    **Adequate**

Manufacture of celecoxib oral solution involves (b) (4)  
(b) (4)

All facilities that will be involved in commercial manufacture and testing of celecoxib and ELYXYB (celecoxib) oral solution are currently acceptable.

*Microbiology:*                    **Adequate**

The product is tested for microbial quality at release and on stability according to compendial methods. The microbiological test methods and acceptance criteria are consistent with USP <1111> recommendations for a non-aqueous and non-sterile oral drug product.:

*Environmental:*                    **Adequate**

The Applicant submitted a claim for categorical exclusion under 21 CFR §25.31(b). Approval of the application would increase use of celecoxib. However, the expected environmental introduction concentration (EIC) is less than 1 part per billion and there are no extraordinary circumstances. **The claim for categorical exclusion is granted.**

*Methods Verification:*

Verification of analytical procedures submitted in the NDA by FDA laboratories was not requested during the review.

### **C. Special Product Quality Labeling Recommendations**

There are no special labeling recommendations from a quality perspective.

### D. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Assay, Stability	x Formulation x Container Closure x Process Parameters	L	(b) (4)	Adequate	
Uniformity of dose/fill volume/deliverable volume	x Formulation x Raw Materials x Process Parameters	L		Adequate	
Physical stability (phase separation)	x Formulation x Raw Materials x Process Parameters	L		Adequate	
Palatability	x Formulation x Raw Materials x Process Parameters	M		Adequate	
Microbial limits	x Formulation x Raw materials x Process parameters x Scale/Equipment/Site	L		Adequate	
Leachables	x Formulation x Container Closure x Raw materials	M		Adequate	

**E. List of Deficiencies for Complete Response**

Not Applicable.

*Application Technical Lead Name and Date:*

Martha R. Heimann, Ph.D. 4/7/2020



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## CHAPTER IV: LABELING

### 1.0 PRESCRIBING INFORMATION

#### Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

Section 11 has been edited to add properly listed excipients. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	ELYXYB	Adequate
Established name(s)	celecoxib	Adequate
Route(s) of administration	Oral	Adequate
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	120 mg, 25 mg/mL	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

### 1.2 FULL PRESCRIBING INFORMATION

#### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE AND ADMINISTRATION section</b>		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE FORMS AND STRENGTHS section</b>		
Available dosage form(s)	oral solution	Adequate
Strength(s) in metric system	25 mg/mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless oral solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

### 1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	ELYXYB, celecoxib	Adequate
Dosage form(s) and route(s) of administration	120 mg oral solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	acesulfame potassium, banana flavor, bubble gum flavor, (b) (4) ethyl alcohol, glycerin, lauroyl polyoxyl-32 glycerides, glyceryl monocaprylate, L-menthol, (b) (4) polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, peppermint flavor, propyl gallate, purified water and sucralose.	Adequate following removal of (b) (4) replacing with glycerin, monoammonium glycyrrhizinate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/therapeutic class	anti-inflammatory	Adequate
Chemical name, structural formula, molecular weight	p-[5-p-tolyl-3-(trifluoromethyl) pyrazol-1-yl]benzenesulfonamide, C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub> S, 381.37.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	pKa is 11 and log P is 3.0	Adequate

**Section 11 (DESCRIPTION) Continued**

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	None	Adequate

**1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)**

Item	Information Provided in the NDA	Assessor's Comments
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s)	Oral solution	Adequate
Strength(s) in metric system	25 mg/mL	Adequate
Available units (e.g., bottles of 100 tablets)	Disposable (b) (4) bottle	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear colorless oral solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

Item	Information Provided in the NDA	Assessor's Comments
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Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not refrigerate or freeze.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	NA	NA
Include information about child-resistant packaging	Stored in glass bottle with a child resistant cap.	Adequate

#### 1.2.4 Other Sections of Labeling

No other sections of the labeling contain product quality information.

#### 1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
<b>Manufacturing Information After Section 17</b>		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Dr. Reddy's Laboratories Limited	A comment has been added to the PI to include the business location.

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): NA**

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label



### 3.2 Carton Labeling



Item	Information Provided in the NDA	Assessor's Comments about Container and Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	ELYXYB, celecoxib	Adequate
Dosage strength	25 mg/mL	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	4.8 mL	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	43598-866-09	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	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)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	Not applicable for prescription drugs.
Bar code	Present	Adequate





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## MICROBIOLOGY

### IQA Review Guide Reference

**Product Background:**

**NDA:** 212157

**Drug Product Name / Strength:** Celecoxib oral solution, 25 mg/mL

**Route of Administration:** Oral solution

**Applicant Name:** Dr. Reddy's Laboratories, Ltd

**Manufacturing Site:** (b) (4)

**Method of Sterilization:** NA, Nonsterile drug product

**Review Recommendation: Adequate**

**Review Summary:** This non aqueous oral solution is tested for microbial quality at release and on stability according to compendial methods

**List Submissions Being Reviewed:** 07/05/2019 and 9/20/2019

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Remarks:** This is a single dose, preservative-free, non-aqueous drug product indicated for the treatment of migraine with or without aura in adults.

**Concise Description Outstanding Issues Remaining:** None

**Supporting Documents:** None

**S Drug Substance** This synthetic drug substance was not reviewed as the microbiological quality is assured during drug product manufacturing.

### **P.1 Description of the Composition of the Drug Product**

- **Description of drug product:** The nonsterile, single dose (b) (4) oral liquid solution (25 mg/mL) is provided in a 10 mL amber glass bottle with child resistant cap.

- **Drug product composition:** The composition is listed below in Table 1 - Drug product composition (Sponsor Table 3.2.P.1.2-1 Module 3.2.P.1)

Table 1: Composition of the Proposed Drug Product

Ingredients	Function	Quality Standard	% w/w	Quantity per dose (mg)
Celecoxib	API	USP	(b) (4)	120.00
Lauroyl polyoxyl-32 glycerides				(b) (4)
(b) (4)				
Glyceryl monocaprylate				
(b) (4)				
Polyoxyl 35 castor oil				
(b) (4)				
Polyoxyl 40 hydrogenated castor oil				
(b) (4)				
Propyl gallate				
L-menthol				
(b) (4)				
Sucralose				
Acesulfame potassium				
(b) (4)				
Glycerin				
(b) (4)				
Ethyl alcohol				
(b) (4)				
Peppermint flavor				
Bubble gum flavor				
Banana flavor				
Purified Water				
<b>Total Weight</b>				

- **Description of container closure system:** The drug product is filled in a 10 mL amber colored glass bottle fitted with a child resistant (CR) cap. The details of primary container and closure system are presented in the table below:

Type of packaging	Name of the component	Material of construction	Manufacturer / Supplier
Amber Glass Container	10 ml amber glass bottle	[Redacted]	(b) (4)
	(b) (4)		
	(b) (4) child resistant closure		
	(b) (4)		

**Reviewer's Assessment: Adequate**

**P.2.5 Microbiological Attributes**

The drug product is nonaqueous, no preservative or AET data is needed.

**P.5 Control of Drug Product**

**P. 5.1 Specification**

The proposed specifications include the following microbiological test methods and acceptance criteria:

- Total Aerobic Microbial Count: NMT [Redacted] (b) (4)
- Total Yeast and Mold Count: NMT [Redacted] (b) (4)
- Absence of [Redacted] (b) (4)

**Reviewer's Assessment: Adequate**  
 The proposed specifications are within recommendations of USP <1111> for a non-aqueous and non-sterile oral drug product.

**P.5.2 Analytical Procedures**

The TAMC, TYMC and the Absence of Specified Organisms are tested following USP <61> and <62>.

**Reviewer's Assessment:** *Adequate.*

(b) (4)

**A Appendices: NA**

**R Regional Information**

***Executed Batch Records***

Executed batch records were submitted for the three exhibit lots, Lots# 100937, 103267 and 103268.

**Reviewer's Assessment: *Adequate***

***Comparability Protocols: NA***

**Reviewer's Assessment: NA**

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

***2.A. Package Insert: NA***

**Reviewer's Assessment: Adequate.** There are no quality microbiology concerns to address in the package insert.

***Post-Approval Commitments: NA***

*List of Deficiencies: None*

***Primary Microbiology Reviewer:***

Samata Tiwari, Ph.D. (11/22/2019)  
Review Microbiologist  
Division of Microbiology Assessment Branch II  
FDA/OMPT/CDER/OPQ/OPMA

***Secondary Reviewer Name:***

Neal Sweeney, Ph.D. (11/22/2019)  
Quality Assessment Lead  
Division of Microbiology Assessment Branch II  
FDA/OMPT/CDER/OPQ/OPMA



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