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APPLICATION NUMBER:

211759Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 211759

Supporting document/s: SDN 7, SDN 13, SDN 20, SDN 23

Applicant's letter date: 09/30/2024, 01/27/25, 04/11/2025, 05/27/2025

Product: Celecoxib Oral Suspension, 10 mg/mL

Indication: Osteoarthritis (OA), Rheumatoid Arthritis (RA),
Ankylosing Spondylitis (AS), Juvenile
Rheumatoid Arthritis (JRA)

Applicant: codaDOSE, Inc.

Review Division: Division of Pharmacology Toxicology for
Neuroscience (DPT-N) with the Clinical Division
of Anesthesiology, Addiction Medicine, and Pain
Medicine (DAAP)

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Template Version: September 1, 2010

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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY.....	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION.....	10
2.1	DRUG	10
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs.....	11
2.3	DRUG FORMULATION	11
2.4	COMMENTS ON NOVEL EXCIPIENTS	12
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	16
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	20
2.7	REGULATORY BACKGROUND	20
3	STUDIES SUBMITTED	21
3.1	STUDIES REVIEWED	21
3.2	STUDIES NOT REVIEWED.....	21
3.3	PREVIOUS REVIEWS REFERENCED.....	21
4	PHARMACOLOGY	21
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	21
6	GENERAL TOXICOLOGY	22
7	GENETIC TOXICOLOGY.....	22
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	22
10	SPECIAL TOXICOLOGY STUDIES.....	23
10.1	EXTRACTABLE/LEACHABLE STUDY.....	23
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	29

1 Executive Summary

1.1 Introduction

On 03/09/2018, codaDOSE, Inc. submitted NDA 211759 for their proposed drug product, Celecoxib Oral Suspension (Vyscoxa®), 10 mg/mL via the 505(b)(2) regulatory pathway, relying on the Agency's previous findings of safety and efficacy for the listed drug (LD) Celebrex® (NDA 020998; approved 12/31/1998). However, FDA issued a Refuse-to-File (RTF) letter dated 04/30/2018. The RTF letter included two nonclinical deficiencies, which noted a lack of a Nonclinical Module 2 and 4 to allow for substantive review and lack of updated labeling in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). Of note, the RTF letter included a clinical deficiency noting that the proposed drug product was not bioequivalent to the LD (i.e., 51% greater C_{max} and 20% greater AUCs for the proposed oral suspension than Celebrex capsule), and that the Applicant should explain how this impacts the safety and efficacy of their drug. A clinical pharmacology comment was also included that requested justification for the greater food effect with the proposed product (i.e., 78% increase in C_{max} and 55 - 58% increases in AUCs) than Celebrex capsule (i.e., 10 – 20% in AUCs).

Given that the product was not bioequivalent to the listed drug and exhibited increased systemic exposure, which raised safety concerns, particularly in light of the Celebrex labeling emphasizing dose-related risks, the company decided to reformulate the product after the RTF. The Applicant resubmitted on 09/30/2024 (SDN 7) and the resubmission addressed the previous nonclinical deficiencies. However, nonclinical review issues were identified with the resubmission and communicated to the Applicant in a Filing Review Issues Identified letter on 12/12/2024. These included an excipient that appeared to exceed levels in other FDA-approved products, a drug product impurity that exceeded ICH Q3B(R2) qualification thresholds, and potentially inadequate leachable data to perform adequate evaluation. Each issue was addressed by the Applicant during the review cycle and are discussed in more detail in this review.

The NDA resubmission also included clinical PK studies in which the Celecoxib Oral Suspension was demonstrated to be bioequivalent to the LD in the fasted state. There was a significant food effect in which the AUC and C_{max} were significantly increased after Celecoxib Oral Suspension administration compared to the LD. The Division consulted Office of New Drug (OND) upper management and ultimately decided to include labeling language and a Medication Guide to inform patients to take the drug on an empty stomach to mitigate for adverse effects related to high celecoxib exposure. Refer to the reviews of the clinical pharmacology and clinical teams and the Division Director review for more details.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the LD, Celebrex.

Celecoxib Oral Suspension includes an excipient that the Applicant identified as magnesium aluminometasilicate that appeared to exceed the level used in FDA-approved products. During the review cycle the Applicant provided additional information to help qualify the levels of this excipient in their drug product. Using a weight-of-the-evidence approach, the level of magnesium aluminometasilicate in the drug product was considered qualified based on a combination of the nonclinical data provided, human experience with the excipient as an (b) (4), and relying on a structurally analogous excipient, which is used in FDA-approved products for a similar duration at higher levels for the proposed route of administration.

The proposed specification for a drug product degradant, Related Compound (b) (4) exceeded the Q3B(R2) guidance qualification threshold. However, in response to an information request by the Agency to justify the safety of the degradant at the proposed limit, the Applicant reduced the specification to be within Q3B(R2) limits. In summary, there are no safety concerns with the drug substance impurities or drug product degradants at the currently proposed specifications.

Additional extractable and leachable data were submitted during the review cycle. The submitted extractables and leachables data did not raise safety concerns from the nonclinical perspective because there were no leachable compounds observed above the appropriate safety concern threshold of (b) (4) mcg/day for general toxicity or (b) (4) mcg/day for genotoxicity.

In summary, the NDA was submitted via the 505(b)(2) pathway relying on the listed drug Celebrex, and an adequate scientific bridge was established via a clinical BA study to qualify celecoxib from a systemic safety perspective. The drug product formulation is adequately qualified for safety for the proposed clinical use. From the nonclinical perspective, there are adequate data to support approval of the NDA.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical pharmacology/toxicology perspective, NDA 211759 may be approved.

1.3.2 Additional Nonclinical Recommendations

None.

Of note, no juvenile animal studies were recommended in the agreed initial pediatric study plan (iPSP). Refer to the Agreed Amended iPSP dated 1/22/2024.

1.3.3 Labeling

The Applicant proposed labeling similar to the reference product, Celebrex. There are no proposed changes to the nonclinical sections 8 and 13 of labeling. Based on the information provided by the Clinical Pharmacology team, the 200 mg dose has been determined to be bioequivalent to the reference drug. Given this finding, it is anticipated that higher doses would exhibit dose-proportional pharmacokinetics. Consequently, it is not necessary to modify the exposure margins in the product labeling. The final label will be based on internal discussion and negotiations with the Applicant. Refer to the Action Package for final labeling language.

Applicant's Proposed Labeling	Reviewer's Recommended changes	Comments and rationale for reviewer's recommended changes
8.1 Pregnancy <u>Risk Summary</u> Use of NSAIDs, including VYSCOX, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of VYSCOX use between about 20 and 30 weeks of gestation and avoid VYSCOX use at about 30 weeks of gestation and later in pregnancy (see <i>Clinical Considerations, Data</i>). <i>Premature Closure of Fetal Ductus Arteriosus</i> Use of NSAIDs, including VYSCOX, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. <i>Oligohydramnios/Neonatal Renal Impairment</i> Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.	8.1 Pregnancy <u>Risk Summary</u> Use of NSAIDs, including VYSCOX, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of VYSCOX use between about 20 and 30 weeks of gestation and avoid VYSCOX use at about 30 weeks of gestation and later in pregnancy (see <i>Clinical Considerations, Data</i>). <i>Premature Closure of Fetal Ductus Arteriosus</i> Use of NSAIDs, including VYSCOX, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. <i>Oligohydramnios/Neonatal Renal Impairment</i> Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.	Vyscova is the Applicant's proposed proprietary name. We defer to the clinical and maternal health review teams regarding clinical labeling language. NSAID class labeling. NSAID class labeling.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose (MRHD) of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD (<i>see Data</i>). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post- implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in	Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose (MRHD) of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD (<i>see Data</i>). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post- implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in	NSAID class labeling. We defer to the clinical and maternal health review teams regarding clinical labeling language.
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clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. <i>Animal data</i> Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24h}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24h} at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥ 50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24h} at 200 mg twice daily for RA). Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24h} at 200 mg twice daily). The effects of celecoxib on labor and delivery in pregnant women are unknown.	clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. <i>Animal data</i> Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24h}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24h} at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥ 50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24h} at 200 mg twice daily for RA). Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24h} at 200 mg twice daily). The effects of celecoxib on labor and delivery in pregnant women are unknown.	Since the 200 mg dose has been determined to be bioequivalent to the reference drug, Celecoxib. It is anticipated that higher doses would exhibit dose-proportional pharmacokinetics. Therefore, the exposure margins remain the same in the product labeling.
8.2 Lactation <u>Risk Summary</u> Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of celecoxib in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based	8.2 Lactation <u>Risk Summary</u> Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of celecoxib in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based	No changes recommended. Language is in line with listed drug.

therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when VYSCOXIA is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYSCOXIA and any potential adverse effects on the breastfed infant from the VYSCOXIA or from the underlying maternal condition.	therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when VYSCOXIA is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYSCOXIA and any potential adverse effects on the breastfed infant from the VYSCOXIA or from the underlying maternal condition.	
8.3 Females and Males of Reproductive Potential <i>Infertility</i> Females Based on the mechanism of action, the use of prostaglandin mediated NSAIDs, including VYSCOXIA, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including VYSCOXIA, in women who have difficulties conceiving or who are undergoing investigation of infertility.	8.3 Females and Males of Reproductive Potential <i>Infertility</i> Females Based on the mechanism of action, the use of prostaglandin mediated NSAIDs, including VYSCOXIA, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including VYSCOXIA, in women who have difficulties conceiving or who are undergoing investigation of infertility.	No changes recommended. Language is in line with listed drug.
12.1 Mechanism of Action Celecoxib has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. Celecoxib is a potent inhibitor of prostaglandin	12.1 Mechanism of Action Celecoxib has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. Celecoxib is a potent inhibitor of prostaglandin	No changes recommended. Language is in line with listed drug.

synthesis <i>in vitro</i>. Celecoxib concentrations reached during therapy have produced <i>in vivo</i> effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	synthesis <i>in vitro</i>. Celecoxib concentrations reached during therapy have produced <i>in vivo</i> effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-times the human exposure as measured by the AUC_{0-24h} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24h} at 200 mg twice daily) for two years. <u>Mutagenesis</u> Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an <i>in vivo</i> micronucleus test in rat bone marrow. <u>Impairment of Fertility</u> Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC_{0-24h}). At ≥50 mg/kg/day (approximately 6-times human exposure based on the AUC_{0-24h}	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-times the human exposure as measured by the AUC_{0-24h} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24h} at 200 mg twice daily) for two years. <u>Mutagenesis</u> Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an <i>in vivo</i> micronucleus test in rat bone marrow. <u>Impairment of Fertility</u> Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC_{0-24h}). At ≥50 mg/kg/day (approximately 6-times human exposure based on the AUC_{0-24h}	Since the 200 mg dose has been determined to be bioequivalent to the reference drug, Celecoxib. It is anticipated that higher doses would exhibit dose-proportional pharmacokinetics. Therefore, the exposure margins remain the same in the product labeling.

at 200 mg twice daily) there was increased preimplantation loss.	at 200 mg twice daily) there was increased preimplantation loss.	
13.2 Animal Toxicology An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.	13.2 Animal Toxicology An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.	No changes recommended. Language is in line with listed drug.

2 Drug Information

2.1 Drug

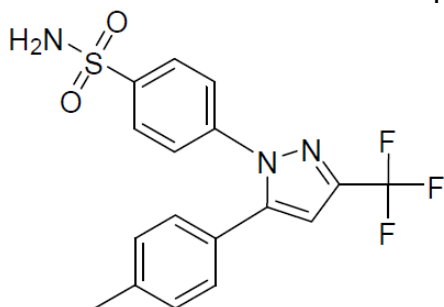
CAS Registry Number: 169590-42-5

Generic Name: Celecoxib

Chemical Name: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Molecular Formula/Molecular Weight: C₁₇H₁₄F₃N₃O₂S/ 381.4

Structure or Biochemical Description



Pharmacologic Class: Nonsteroidal anti-inflammatory drug (NSAID)

2.2 Relevant INDs, NDAs, BLAs and DMFs

VYSCOXA™ was developed under IND 122698. This NDA was submitted via the 505(b)(2) pathway relying on the listed drug Celebrex (NDA 020998).

Application	Drug Name	Route	Strength	Status	Indication
NDA 020998	Celebrex ®	Oral	Capsule: 50, 100, 200, and 400 mg	Approved 12-13-1998	• Osteoarthritis (OA) • Rheumatoid Arthritis (RA) • Ankylosing Spondylitis (AS) • In pediatric patients two years and older for Juvenile Rheumatoid Arthritis (JRA) • Acute Pain • Primary Dysmenorrhea
IND 122698	Celecoxib	Oral	Oral suspension 10 mg/mL	Active 09/08/2016	Same as LD (note that NDA 211759 does not include all indications of the listed drug, i.e., excludes acute pain and primary dysmenorrhea)

DMF	Subject	Holder	Status
(b) (4)	(b) (4)	(b) (4)	Active
Type II			08-30-2012
(b) (4)			Active
Type IV			03-11-1998

2.3 Drug Formulation

With this resubmission, the Applicant has reformulated their Celecoxib Oral Suspension compared to the formulation submitted with the initial NDA to try to achieve bioequivalence to the listed drug (LD), Celebrex. The proposed drug product is a white, opaque, (b) (4) oral suspension. The drug product composition and function of each excipient are provided in table below.

Component	(b) (4) Code	Reference	Function	Weight (per Batch)	Weight (mg per 1 mL)	Weight (%w/v)
Celecoxib	(b) (4)	USP	Active Ingredient	(b) (4)	10.00 mg	1.0%
Xanthan Gum (b) (4)	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Citric Acid Anhydrous	(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methylparaben	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propylparaben	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glycerin	(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Aluminummetasilicate (b) (4)	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified Water	(b) (4)	USP/EP	(b) (4)	(b) (4)	QS	QS
Sodium Hydroxide	(b) (4)	NF	pH adjustment	N/A	N/A	N/A
Hydrochloric Acid	(b) (4)	NF	pH adjustment	N/A	N/A	N/A
Total	(b) (4)			(b) (4)	(b) (4)	100%
(b) (4) Per supplier certificate of analysis , the product meets EP and USP requirements (b) (4)						

Comparison of the proposed drug product and LD attributes are shown in the Applicant's table below.

Product Attributes	Celecoxib Oral Suspension	Reference Listed Drug
Physical Description	White, opaque, (b) (4) suspension	200 mg capsule for oral administration.
Dosage Form	Suspension	Capsule
Route of Administration	Oral	Oral
Active Ingredient(s)	Celecoxib	Celecoxib
Proprietary Name	VYSCOXIA (proposed)	CELEBREX®
Strength(s)	10 mg/mL	50 mg, 100 mg, 200 mg, and 400 mg
Indication(s)	Relief of the signs and symptoms of: - Osteoarthritis (OA) - Rheumatoid Arthritis (RA) - Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older. - Ankylosing Spondylitis (AS)	Relief of the signs and symptoms of: - Osteoarthritis (OA) - Rheumatoid Arthritis (RA) - Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older - Ankylosing Spondylitis (AS) Management of Acute Pain (AP) in adults Treatment of Primary Dysmenorrhea (PD)
Rx/OTC	Rx	Rx

2.4 Comments on Novel Excipients

The celecoxib drug product contains, citric acid anhydrous, sodium citrate dihydrate, sodium hydroxide and hydrochloric acid to adjust pH. These excipients are commonly used in FDA-approved products and are considered qualified.

ADEQUACY OF DRUG PRODUCT FORMULATION

Ingredient	dose (mg/day)	Oral, Inactive Ingredient Database (IID) Maximum Daily Exposure, mg	Comment on Adequacy
Celecoxib	(b) (4)	N/A	Covered by referenced drug Celebrex
Xanthan Gum	(b) (4)	(b) (4)	Covered by approved FDA products for oral administration for chronic use
Methylparaben			Covered by approved FDA products for oral administration for chronic use
Propylparaben			Covered by approved FDA products for oral administration for chronic use
Glycerin			Covered by approved FDA products for oral administration for chronic use
Sucralose			Covered by approved FDA products for oral administration for chronic use
Magnesium Aluminometasilicate		--	See below

The formulation includes an excipient that the Applicant identified as magnesium aluminometasilicate, which is also known as (b) (4) or more specifically (b) (4). At the time of the initial submission the excipient was considered new because: 1) neither the term magnesium aluminometasilicate nor (b) (4) are included in the publicly available Inactive Ingredient Database (IID) or internal Inactive Ingredient Report (IIR); 2) the CAS number from the manufacturer's website for (b) (4) did not match any excipient in the IIR; 3) searching magnesium aluminometasilicate in the FDA's Global Substance Registration System (GSRS) resulted in (b) (4) as the best match but the MDE for (b) (4) in FDA approved products (b) (4) mg) is lower than the MDE of magnesium aluminometasilicate (b) (4) g) in the current formulation; and 4) despite not being listed in the IIR, magnesium aluminometasilicate is in FDA drug products approved for similar duration of use at lower levels (maximum daily exposures up to (b) (4) mg) than in the proposed drug product (MDE of (b) (4) mg).

The Applicant included a Letter of Authorization to a DMF (b) (4) for the excipient and a summary document regarding pharmacological, toxicological, and clinical data for the excipient in the initial submission. This included a summary of the development of (b) (4), including summaries of both clinical and nonclinical data. However, the data provided was not considered adequate since: 1) the nonclinical study reports referenced in the summary documents were not provided; 2) the referenced nonclinical studies did not cover all relevant toxicology endpoints

recommended in the guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (specifically the reproduction and developmental data); and 3) the DMF did not include reviewable nonclinical data to support the safety of the excipient.

The lack of adequate qualification for magnesium aluminometasilicate based on levels in FDA-approved products and the submitted data was communicated to the Applicant in the 74-day letter (see DARRTS; 12/12/2024) with a request for additional information to justify the safety of the excipient. In response, the Applicant submitted a risk assessment on 01/27/2025 (SDN 13) and provided copies and translations of the study reports cited. Notably, the risk assessment referenced nonclinical toxicology studies with various chemical names (e.g., (b) (4) (b) (4)) and (b) (4) that differ from the name of the excipient used in the proposed product (magnesium aluminometasilicate). An Information Request was sent to the Applicant on 05/13/2025 asking for additional information regarding the different terminologies used and the relevance of those compounds for supporting the safety of magnesium aluminometasilicate in their drug product.

The risk assessment provided by the Applicant summarized findings across eight nonclinical toxicology studies that administered a form of (b) (4) to mice, rats, dogs, monkeys, or rabbits. The duration of exposure in these studies ranged from single doses to just over two years of repeat dosing. One of the studies in mice evaluated effects on reproductive and developmental toxicity and dosed from Gestational Day (GD) 7-12. An overview of these studies is provided in the table below.

Table 1. Summary of toxicological studies of magnesium aluminosilicate.

Assay	Species	Route	Exposure	Effect	Reference
Acute Toxicity	Mouse	Oral	Single	LD ₅₀ > 16 g/kg	Ueda, 1965
	Rat	Oral	Single	LD ₅₀ > 5 g/kg	Kimura et al., 1967
	Rat	Intraperitoneal	Single	LD ₅₀ > 5 g/kg	
	Mouse	Oral	Single	LD ₅₀ > 5 g/kg	
	Mouse	Intraperitoneal	Single	LD ₅₀ > 5 g/kg	
Repeat Dose Toxicity	Mouse	Oral	14 days	NOAEL = 6000 mg/kg	Sakai et al., 1974
	Rat	Oral	30 days	NOAEL = 1200 mg/kg	Gibson et al., 1965
	Dog	Oral	2 months	NOAEL = 5000 mg/kg	Roissier, 1962
	Monkey	Oral	1 month	NOAEL = 2.4 g/kg	Newberne, 1967
	Rat	Oral	27 months	NOAEL = 200 mg/day	Kimura et al., 1967
	Rabbit	Oral	27 months	NOAEL = 50 mg/day	
	Monkey	Oral	3-6 months	NOAEL = 1200 mg/kg	Newberne, 1969
	Mouse	Oral	1 year	NOAEL = 7% in diet	Matsui et al., 1968
	Rat	Oral	1 year	NOAEL = 7% in diet	
Reproductive/Developmental	Mouse	Oral	GD 7-12	NOAEL _{Maternal} = 6000 mg/kg NOAEL _{Developmental} = 6000 mg/kg	Sakai et al., 1974

No significant toxicological findings were reported in any of the studies despite dosing up to 27 months. The one exception was findings of reduced body weight, decreased activity, and coarse fur starting on Day 3, with recovery by Day 10 in mice receiving 6000 mg/kg. Lower doses (1000 and 3000 mg/kg) induced only slight weight loss without clinical signs. Even assuming a conservative NOAEL of 3000 mg/kg in this

study, the NOAEL results in a human equivalent dose (HED) of ~ (b) (4) g based on body surface area scaling assuming a 60 kg individual, which is ~ (b) (4) times the MDE of the excipient in the drug product. The NOAELs from the longest term study (27 months) were 200 mg/kg (the highest dose tested; note the NOAEL in the table above for rabbit was 50 mg/kg but no findings were observed up to 200 mg/kg in rabbits and appears to be an error in the Applicant's table) in rabbits and rats which result in HEDs of (b) (4) ((b) (4) x the MDE of the excipient) and (b) (4) mg (b) (4) x the MDE of the excipient), respectively, based on body surface area scaling assuming a 60 kg individual. An even higher margin for chronic exposure can be achieved from the 1-year study in rats which tested higher doses with no effects observed up to (b) (4) g (HED of (b) (4) g or (b) (4) times the MDE from the drug product).

The Applicant also noted that (b) (4) dosed up to (b) (4) g/day. The Applicant provided the packaging insert for the antacid which indicates (b) (4) at the MDE for magnesium aluminometasilicate would be (b) (4) mg.

Interestingly, the (b) (4) is also known as (b) (4). The CAS number provided by the manufacturer for the excipient is (b) (4) which is associated with (b) (4) (b) (4) which is confusing because the Applicant indicates that (b) (4) includes (b) (4) and should therefore be in (b) (4) which corresponds to how it is identified in the (b) (4). (b) (4) is also known as (b) (4) according to the GSRS and the chemistry database PubChem of the National Institutes of Health (<https://pubchem.ncbi.nlm.nih.gov/>). This is relevant because (b) (4) is in FDA-approved oral products for chronic use at levels that are higher than in the current formulation (e.g., MDE of (b) (4) mg as compared to the MDE for (b) (4) of (b) (4) mg). We consulted the FDA Computational Toxicology Consultation Service (CTCS) for assistance in differentiating these similar chemicals to see if it is reasonable to bridge data from one compound to the other. Overall, it appears that the terminology of these (b) (4) and (b) (4) has not been entirely consistent and the exact nature of all the compounds is not completely clear. Based on the information available they all appear to contain various amounts of (b) (4) and (b) (4) that appear to differ subtly in their (b) (4) and (b) (4) status. The CTCS consult supported that the compounds would all be reasonable (b) (4) for each other as they contain similar components only differing in the ratio of the components.

Taken together, the levels of magnesium aluminometasilicate in the drug product, resulting in an MDE of (b) (4) mg, is considered qualified based on a weight of the evidence approach considering the following: 1) toxicity studies with magnesium aluminometasilicate did not result in any toxicity findings up to doses of (b) (4) g in rats (HED of ~ (b) (4) g or (b) (4) times the MDE from the drug product) for up to 1 year and (b) (4) mg/kg (the highest dose tested; HED of ~ (b) (4) g or (b) (4) x the MDE from the drug product) up to 2 years; 2) the excipient has been used as an (b) (4) with an MDE of (b) (4) mg/day (b) (4) times the MDE in the formulation); 3) the excipient has been used in FDA approved drugs products of similar durations up to (b) (4) mg; (b) (4) the

acceptable (b) (4) has been used in FDA approved products up to (b) (4) mg for chronic use and at higher levels for drugs approved for shorter durations. While the toxicity data provided by the Applicant was generally limited in that it did not address the full reproductive/developmental endpoints and would not be sufficient alone, the other points considered in the weight of the evidence would address the lack of the full reproductive/developmental including the human experience as an antacid, its use in FDA approved products as magnesium aluminometasilicate (albeit at lower levels), and the higher levels of the acceptable (b) (4) in FDA-approved products.

2.5 Comments on Impurities/Degradants of Concern

Drug Product

The resubmission following the Refuse-to-File (RTF) action included the proposed drug product (DP) specifications described in the table below. Of note, the proposed specification for Related Compound (b) (4) at NMT (b) (4)% exceeds the appropriate qualification threshold of NMT (b) (4)% recommended in the Q3B(R2) guidance based on the maximum recommended daily dose of 400 mg.

In the 74-Day Letter, sent on 12/12/2024, we included the following comment:

Your proposed drug product specification for the degradant (b) (4) at NMT (b) (4)% exceeds the appropriate qualification threshold of NMT (b) (4)% as recommended in the guidance, Q3B(R2) Impurities in New Drug Products (August 2006) based on the maximum daily dose (MDD) of celecoxib at 400 mg/day. We acknowledge your justification that (b) (4)% was chosen to align with the USP for the (b) (4). However, this is not an adequate justification alone. Tighten your drug product specification to align with Q3B(R2) guidance qualification threshold of NMT (b) (4) or provide additional justification based on data to qualify the safety of the (b) (4) purity. In order to provide adequate qualification:

- Conduct a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- In addition, conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90 days should be completed. Refer to the ICH guidances for industry: Q3B(R2) Impurities in New Drug Products.
- Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: ANDAs: Impurities in Drug Products

Celecoxib Oral Suspension Specifications (b) (4)

Test	Procedure	Specification
Appearance/Description	ATM 1100	White, opaque, (b) (4) suspension
pH	USP <791>	(b) (4)
Viscosity	ATM 3603	(b) (4) cPs
Specific Gravity	USP <841>	(b) (4)
Identification by PDA ¹	ATM 3643	The UV (b) (4) nm spectrum of the Celecoxib peak corresponds to that of the Standard solution, as obtained by the Assay.
Identification by HPLC ¹	ATM 3643	The retention time of the Celecoxib peak corresponds to that of the standard solution, as obtained by the Assay.
Assay	ATM 3643	Celecoxib: (b) (4) %
Preservative Assay	ATM 3643	Methylparaben: (b) (4) %
		Propylparaben: (b) (4) %
Uniformity of Dosage Units ¹	USP <905>	L1: AV ≤ (b) (4)
		L2: AV ≤ (b) (4)
Redispersibility	ATM 3643	NMT (b) (4) % difference in Celecoxib assay between top and bottom samples
Assay for Impurities	ATM 3643	Each Individual Unspecified Impurities: NMT (b) (4) %
		Related Compound (b) (4) NMT (b) (4) %
		Related Compound (b) (4) NMT (b) (4) %
		Total Impurities: NMT (b) (4) % ²
Weight Loss Rate ³	ATM 3638	NMT (b) (4) test containers exceeds (b) (4) % per year percentage of weight loss and does not exceed (b) (4) % per year in any of them
Deliverable Volume ¹	USP <698>	Stage I: The average volume from (b) (4) containers is NLT (b) (4) % of the labeled volume and the volume of (b) (4) container is less than (b) (4) % of the labeled volume.
		Stage II: The average volume from (b) (4) containers is NLT (b) (4) % of the labeled volume and the volume from NMT (b) (4) containers is less than (b) (4) % of the labeled volume, but NLT (b) (4) % of the labeled volume.

In a response to the 74-day letter comments (SDN 13; submitted on 1/27/25), the Applicant revised the drug product (DP) specification for the degradant to NMT (b) (4), to be within the with the Q3B(R2) guidance qualification threshold. The revised specification is shown in the table below.

Revised Celecoxib Oral Suspension Specifications

(b) (4)

Test/Procedure	Specification	Justification
Appearance/Description ATM 1100	White, opaque, (b) (4) suspension	Based on Visual Observation
pH USP <791>	(b) (4)	Based on Development, Release, and Stability Data
Viscosity ATM 3603	(b) (4)	Based on Development, Release, and Stability Data
Specific Gravity USP <841>	(b) (4)	Based on Development, Release, and Stability Data
Identification by PDA ¹ ATM 3643	The UV (b) (4) nm spectrum of the Celecoxib peak corresponds to that of the Standard solution, as obtained by the Assay.	Based on Development, Release, and Stability Data
Identification by HPLC ¹ ATM 3643	The retention time of the Celecoxib peak corresponds to that of the standard solution, as obtained by the Assay.	Based on Development, Release, and Stability Data
Assay ATM 3643	Celecoxib: (b) (4) %	Based on Development, Release, and Stability Data
(b) (4) Assay ATM 3643	Methylparaben: (b) (4) % Propylparaben: (b) (4) %	Based on Development, Release, and Stability Data
Content Uniformity ¹ USP <905>/ ATM 3643	L1: AV ≤ (b) (4) L2: AV ≤ (b) (4)	Based on USP <905>
Redispersibility ATM 3643	NMT (b) (4) % difference in Celecoxib assay between top and bottom samples	Based on Development, Release, and Stability Data
Assay for Impurities ATM 3643	Each Individual Unspecified Impurities: NMT (b) (4) %	Based on Development, Release, Stability Data, and the USP monograph for Celecoxib drug substance. Refer to Table 23, Table 24, and Table 25
	Celecoxib Related Compound (b) (4) NMT (b) (4) %	
	Celecoxib Related Compound (b) (4) NMT (b) (4) %	
	Total Impurities: NMT (b) (4) % ²	
Weight Loss Rate ³ ATM 3638	NMT (b) (4) test containers exceeds (b) (4) % per year percentage of weight loss and does not exceed (b) (4) % per year in any of them	Based on USP <671>

Drug Substance

The drug substance (DS) specifications are shown in the table below.

Celecoxib Drug Substance Specifications (b) (4) and (b) (4)

Test	(b) (4) Method	(b) (4) Specification	USP Specification	(b) (4) Specification
Description	ATM 1100	White or almost white, (b) (4) or (b) (4) powder	N/A	White or almost white, (b) (4) powder.
Identification A by IR	USP	The IR spectrum of the preparation of the sample exhibits maxima only at the same wavenumbers as that of the appropriately prepared corresponding USP Reference Standard	Conforms to standard	The infrared absorption spectrum of the sample must be concordant with the standard spectrum
Identification B by HPLC	USP	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay	The retention time of the major peak of the sample solution corresponds to that of the Standard solution
Residue on Ignition	USP	NMT (b) (4) %	NMT (b) (4) %	NMT (b) (4) % w/w
Water Determination	USP	NMT (b) (4) %	NMT (b) (4) %	NMT (b) (4) % w/w
Assay	USP	(b) (4) % on the anhydrous basis	(b) (4) % on the anhydrous basis	Between (b) (4) % w/w on the anhydrous basis
Organic Impurities	USP	Celecoxib related compound (b) (4) NMT (b) (4) % Celecoxib related compound (b) (4) NMT (b) (4) % Individual unspecified impurity: NMT (b) (4) % Total impurities: NMT (b) (4) %	Celecoxib related compound (b) (4) NMT (b) (4) % Celecoxib related compound (b) (4) NMT (b) (4) % Individual unspecified impurity: NMT (b) (4) % Total impurities: NMT (b) (4) %	Celecoxib related compound (b) (4) NMT (b) (4) % Celecoxib related compound (b) (4) NMT (b) (4) % Individual unspecified impurity: NMT (b) (4) % Total impurities: NMT (b) (4) %
Residual Solvents	USP <467>	Meets the requirements of USP <467> Residual Solvents ³ (b) (4) NMT (b) (4) ppm NMT (b) (4) ppm	Per USP <467>: (b) (4) NMT (b) (4) ppm NMT (b) (4) ppm	(b) (4) NMT (b) (4) ppm (b) (4) NMT (b) (4) ppm
Loss on Drying ⁴	USP <731>	NMT (b) (4) %	N/A	NMT (b) (4) % w/w
Particle Size	001/47001/28	(b) (4) NLT (b) (4) μm between (b) (4) μm to (b) (4) μm NMT (b) (4) μm	N/A	(b) (4) NLT (b) (4) μm between (b) (4) μm to (b) (4) μm NMT (b) (4) μm
Test	(b) (4) Method	(b) (4) Specification	USP Specification	(b) (4) Specification
Genotoxic Impurity	NPLC-100.5	(b) (4) NMT (b) (4) ppm	N/A	(b) (4) NMT (b) (4) ppm

A supplier statement indicating compliance with ICH Q3C is on file.

Of note, Impurity (b) (4) exceeds the Q3A(R2) guidance qualification threshold of NMT (b) (4) . This impurity is also present in the drug product, for which the specification has been tightened to (b) (4) %.

Although the drug substance impurity level exceeds the Q3A(R2) guidance limit, the impurity is being monitored in the drug product and the drug product specification for this impurity is within the limits recommended by the Q3B(R2) guidance. Based on these considerations, there are no significant safety concerns identified at this time from a pharmacology/toxicology standpoint.

In addition, the specifications note there is a genotoxic impurity related to synthesis with a limit of NMT (b) (4) ppm. The potential exposure to this impurity based on the maximum daily dose of the drug is (b) (4) mcg/day, which is below the acceptable daily intake of a mutagenic impurity at (b) (4) mcg/day for chronic use per the M7(R1) guidance. The batch data indicate that the impurity was not detected. Therefore, the impurity does not pose a safety concern at the limit proposed.

2.6 Proposed Clinical Population and Dosing Regimen

The draft label states in the Dosage and Administration section to use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. The dosing regimen is described for the following proposed patient populations:

- Osteoarthritis (OA): 200 mg (20 mL) once daily or 100 mg (10 mL) twice daily.
- Rheumatoid Arthritis (RA): 100 mg (10 mL) to 200 mg (20 mL) twice daily.
- Ankylosing Spondylitis (AS): 200 mg (20 mL) once daily single dose or 100 mg (10 mL) twice daily. If no effect is observed after 6 weeks, a trial of 200 mg (20 mL) twice daily may be of benefit.
- Juvenile Rheumatoid Arthritis (JRA): 50 mg (5 mL) twice daily in patients 10 kg to 25 kg. 100 mg (10 mL) twice daily in patients more than 25 kg.

2.7 Regulatory Background

- PIND 122698 meeting minutes dated 08/25/2014
- IND 122698 submitted 08/09/2016; allowed to proceed; refer to 30-day nonclinical safety review dated 09/09/2016
- NDA 211759 submitted 03/09/2018
- Refuse to File (RTF) Letter issued 04/30/2018
- Type A Meeting Minutes issued 07/16/2018
- NDA 211759 Resubmission after RTF submitted 09/29/2024
- Filing Issues Identified Letter issued 12/12/2024
 - Nonclinical comments:
 - The level of the excipient magnesium aluminometasilicate (b) (4) in your drug product at (b) (4) mg/day based on the maximum recommended daily dose (MDD) exceeds the maximum daily exposure in approved drug products as listed in the FDA inactive ingredient database (IID). We acknowledge that you provided a document summarizing the excipient's pharmacological, toxicological, and clinical data, as well as a Letter of Authorization (LOA) to reference the Drug Master File (DMF) for the excipient. However, we note the following review issues with the information provided: a) The nonclinical study reports referenced in your document were not provided, and the conclusions cannot be independently verified. b) The referenced nonclinical studies do not cover all relevant toxicology studies recommended in the guidance for industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients² to qualify a new excipient. For example, based on preliminary review, it appears that several developmental and reproductive toxicity studies, including fertility and early embryonic studies in male and female rodents, a pre- and postnatal development study, and an embryofetal development study in rabbits, were not included. c) The DMF for the excipient does not appear to include nonclinical data to address the safety of the excipient.

- We note that your leachable data for your new formulation only appears to include a single batch tested at 5 months. Leachable analyses should evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at each timepoint over the course of your stability studies in order to identify trends in leachable levels over time (including early, middle, and late time points). The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product. The adequacy of the leachable information submitted will be determined during the review cycle.

3 Studies Submitted

3.1 Studies Reviewed

1. Qualification of (b) (4) as an Excipient in Celecoxib Oral Suspension (SDN 13)
2. (b) (4) Summary Data (SDN 23)

These risk assessments were submitted to support the safety of the excipient magnesium aluminometasilicate and are discussed in Section 2.4 of this review.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

No new nonclinical pharmacology studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the listed drug (LD) Celebrex and will include information regarding the mechanism of action from the LD in section 12 of labeling. The Applicant also provided a literature review that summarizes the available pharmacology information for celecoxib.

5 Pharmacokinetics/ADME/Toxicokinetics

No new nonclinical pharmacokinetics/ADME/toxicokinetics studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the listed drug (LD) Celebrex. The Applicant provided a literature review that summarizes the available ADME information for celecoxib.

The NDA resubmission included clinical PK studies in which Celecoxib Oral Suspension was demonstrated to be bioequivalent to the LD in the fasted state. There was a

significant food effect in which the AUC and $C_{\max}$ was significantly increased after Celecoxib Oral Suspension administration compared to the LD. The Division consulted OND upper management and ultimately decided to include labeling language and a Medication Guide to inform patients to take the drug on an empty stomach to mitigate for adverse effects related to high celecoxib exposure. Refer to the reviews of the clinical pharmacology and clinical teams and the Division Director review for more details.

6 General Toxicology

No new general toxicology studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the listed drug (LD) Celebrex. Clinical bioavailability studies were conducted to establish a bridge to the systemic safety of the LD.

7 Genetic Toxicology

No new genetic toxicology studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the listed drug (LD) Celebrex and will include genetic toxicology information from the LD in section 13 of labeling.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted with this NDA. The application was submitted via the 505(b)(2) regulatory pathway relying on the Agency's findings for the listed drug (LD) Celebrex and will include reproductive and developmental toxicology information from the LD in section 8 and 13 of labeling.

The NDA resubmission included a draft label updated to comply with the PLLR format and is consistent with the listed drug label, which includes animal carcinogenicity data and genetic and reproduction toxicology information. As part of the submission the Applicant submitted a nonclinical literature review describing their search strategy, a list of articles reviewed, and a rationale for why recent published information is not appropriate for the label.

The Applicant provided an overview of recent developments in the understanding of celecoxib's reproductive toxicity. The Applicant outlines the methodology used for their literature search. Specifically, they limited their review to publications from 2019 onward, citing reliance on existing data from Celebrex as part of the Elyxyb 505(b)(2) NDA. The Applicant assumed that literature published up to 2018 had already been reviewed and considered during that prior evaluation. The search yielded only one relevant study on the reproductive toxicity of celecoxib: Ali et al. (2022). In this study, celecoxib (but not diclofenac or naproxen) was found to "exacerbate"—that is, maintain or prolong—the preeclamptic rise in systolic blood pressure in preeclamptic pregnant rats. Despite this observation, the Applicant concludes that an update to the product label is not currently warranted, pending confirmation of the findings by an additional

study. We agree that the findings from the published study should not be included in the label.

10 Special Toxicology Studies

10.1 Extractable/Leachable study

The NDA resubmission included extractable leachable studies to justify the safety of the container closure system (CCS). The CCS consists of a 16 oz (b) (4) dark amber (b) (4) (b) (4) bottle (b) (4) child resistant (b) (4) closure (b) (4) as indicated in the table below.

Component	(b) (4) Code	Specifications and Drawing	Supplier Certificate of Compliance	(b) (4) Certificate of Compliance
16 oz (b) (4) dark amber, (b) (4) bottle	(b) (4)	BTLP-0056-00	P220885	PC00017999
			P194813	PC00009515
(b) (4)	(b) (4)	CAP-0072-02	84152260	PC00017265

The CCS component materials are described in the table below.

Component	Material	Manufacturer	DMF
Bottle (b) (4)	Bottle: 16 oz (b) (4) dark amber, (b) (4) bottle		(b) (4)
	- GMP Statement - Elemental Impurity Statement		
	(b) (4)		
	(b) (4) General Specifications (b) (4) Regulatory Information Sheet (b) (4) Certification of Analysis - Explanation Letter (b) (4) FDA - Compliance Letter		
	(b) (4)		
Closure (b) (4)	- Technical Data Sheet - Regulatory Statement		
	Closure (b) (4)		
	(b) (4)		
	Regulatory Information		
	(b) (4)		
	Technical Data Sheet		
	(b) (4)		
Closure (b) (4)	(b) (4)		
	(b) (4)		
	(b) (4)		
	Technical Product Sheet		
	(b) (4)		
Closure (b) (4)	(b) (4) Technical Data Sheet		
	(b) (4)		

Container/ Closure with (b) (4)

Configuration	Component	Description	Material Used
16 oz Dark Amber (b) (4) Container and Child (b) (4) Resistant (b) (4) foil induction seal liner	Container	16 oz (b) (4) dark amber, (b) (4) (b) (4) bottle (b) (4) Code: (b) (4)	Vendor name: (b) (4) (b) (4) Description: BTL (b) (4) amber (b) (4) 16oz (b) (4) Material: (b) (4) (b) (4) (b) (4)
	Closure	Cap (b) (4) (b) (4) Foil Induction Seal (b) (4) Code: (b) (4)	Vendor name: (b) (4) (b) (4) (b) (4) Material: (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

To address supply chain issues with the (b) (4) one additional closure from (b) (4) was assessed for use with the (b) (4) 16 oz. (b) (4) bottle for Celecoxib Oral Suspension as shown in the table

(b) (4) Foil Induction Seal (b) (4)		
Component	Description	Material Used
Closure	(b) (4) Foil Induction Seal (b) (4) (b) (4)	Vendor name: (b) (4) (b) (4) Closure (b) (4) Material: (b) (4) (b) (4) (b) (4) (b) (4) Same (b) (4)

The following comment was included in the 74-Day Letter, sent on 12/12/2024:

“We note that your leachable data for your new formulation only appears to include a single batch tested at 5 months. Leachable analyses should evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at each timepoint over the course of your stability studies in order to identify trends in leachable levels over time (including early, middle, and late time points). The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product. The adequacy of the leachable information submitted will be determined during the review cycle.”

Following review, the extractable and leachable studies were considered acceptable from the CMC perspective. To calculate an analytical evaluation threshold (AET), the Applicant applied a safety concern threshold (SCT) of (b) (4) mcg/day which is appropriate based on the proposed chronic indications. Considering the uncertainty of the analysis method, an additional uncertainty factor of (b) (4) was applied to calculate the final value of AET, as shown below.

Table 13: Analytical Evaluation Limit for Celecoxib Oral Suspension, 10 mg/mL

Safety Concern Threshold (SCT) for AET	(b) (4) µg/day
Safety Concern Threshold (SCT) for QT	(b) (4) µg/day
Max administered daily dose	400 mg/day
Unit Filling Volume	473 mL
Doses per Day	2
Labeled Doses per Container	(b) (4)
Analytical Evaluation Threshold (AET)	(b) (4) µg/mL
Estimated Qualification Threshold (QT)	(b) (4) µg/mL
Uncertainty Factor (UF)	(b) (4)
Analytical Evaluation Threshold (AET) with UF	(b) (4) µg/mL

Component	Manufacturer / Lot Number	Description
Container (Bottle)	(b) (4) Component Name: BTL (b) (4) (b) (4) AMBER 16OZ (b) (4) (b) (4)	Bottle Description: (b) (4) (b) (4) (b) (4) Material: (b) (4) (b) (4) AMBER (b) (4) COLOR (b) (4)
Closure (Cap)	(b) (4) Code # (b) (4) Client Code Number: (b) (4) Lot# (b) (4) SM# (b) (4)	Cap Description: (b) (4) (b) (4) (b) (4) (b) (4)
(b) (4)	Product Code Number: (b) (4) Lot (b) (4) SM# (b) (4)	Label Description: (b) (4) (b) (4) Material Description: (b) (4) (b) (4) (b) (4)

For the leachable studies, three batches were tested at 29 months and one batch tested at 17 months (refer to the table below).

Available Leachable Data

Lot#	Leachables Testing Time Points
2207442	29 months
2207447	29 months
2207449	17, 29 months

In SDN 20, submitted on 04/11/2025, an extractables screening was performed using the drug product placebo as the extraction media to simulate worst-case conditions. No tentatively identified compounds were observed above the AET of (b) (4) mcg/mL in the drug product formulation at 17 months. Additional leachables screening was conducted on three different lots of the drug product at 29 months. No tentatively identified compounds were observed above the AET of (b) (4) mcg/mL in any of the 29-month drug product lots. While this testing regimen does not fully align with the general recommendation of three batches at early, middle, and late timepoints, the CMC reviewer indicated that the leachable methods and data were adequate from the CMC perspective.

Therefore, there is minimal risk from leachables arising from the container closure system and no toxicological risk assessments were warranted from a nonclinical perspective.

11 Integrated Summary and Safety Evaluation

In a Filing Review Issues Identified letter on 12/12/2024, nonclinical review issues were identified with the resubmission and communicated to the Applicant. These included an excipient, magnesium aluminometasilicate, that appeared to exceed levels in other FDA-approved products, a drug product impurity that exceeded Q3B(R2) guidance qualification thresholds, and potentially inadequate leachable data to perform adequate evaluation.

The excipient magnesium aluminometasilicate, also known as (b) (4) was considered new since it appeared to exceed the levels in FDA-approved products as either (b) (4) in the Inactive Ingredient Report (IIR) or as magnesium aluminometasilicate through the FDA's Global Substance Registration System (GSRS). The Applicant attempted to justify the safety of the excipient based on nonclinical data which they submitted for review. The nonclinical data generally supported that the excipient did not result in significant toxicity, even following chronic dosing up to 27 months. The NOAELs from the longest-term study (27 months) provided safety margins of (b) (4) the MDE of the excipient based on body surface area scaling assuming a 60 kg individual. An even higher margin for chronic exposure was achieved from the 1-year study in rats of (b) (4) the MDE of the excipient based on body surface area scaling assuming a 60 kg individual.

Despite the lack of significant toxicological findings, there are some limitations to the data provided by the Applicant. The studies were conducted prior to GLP regulations, and the study reports are limited in detail as compared to a modern day GLP study report. Further, the data provided does not cover all relevant toxicological endpoints as indicated in the excipient guidance. For example, the only reproductive/developmental toxicology data was from an embryo-fetal developmental study with dosing from Gestational Day 7 to 12 that was described as a pre- and post-natal developmental study by the Applicant.

Additional data was considered to bolster the existing data and lack of full reproductive/developmental toxicology. This included considering the human experience with the excipient as an Over-the-counter (OTC) antacid and considering similar compounds, such as (b) (4). In terms of human experience, the Applicant noted that (b) (4) is used as an antacid up to (b) (4)/day in Japan. The Applicant also provided a packaging insert for a version of (b) (4) sold in America and it indicated that magnesium aluminometasilicate can be used up to (b) (4) mg day.

FDA's Computational Toxicology Consultation Service (CTCS) was consulted to see if similar compounds would be reasonable structural analogs to support the safety of magnesium aluminometasilicate. This was necessary since many similar terms and structures have been associated with the excipient in various sources and whether they were chemically similar to the excipient or the excipient itself was unclear. CTCS looked at (b) (4) (CAS (b) (4) the same CAS as the excipient), (b) (4) (CAS (b) (4) the primary terminology used in the IIR and

structurally similar), (b) (4) (CAS (b) (4) another terminology associated with magnesium aluminometasilicate), and (b) (4) (Cas (b) (4) another terminology used in the IIR that was structurally similar). CTCS concluded that the (b) (4) considered were acceptable since they all contained the same components as magnesium aluminometasilicate, only differing in the ratio. (b) (4) is found in FDA-approved products for chronic duration at higher levels than the MDE for magnesium aluminometasilicate in the current drug product.

Taken together, the levels of magnesium aluminometasilicate in the drug product, resulting in an MDE of (b) (4) mg, is considered qualified based on a Weight of the Evidence Approach considering the following: 1) toxicity studies with magnesium aluminometasilicate did not result in any toxicity findings up to doses of (b) (4) g in rats (HED of (b) (4) g or (b) (4) times the MDE from the drug product) for up to 1 year and (b) (4) mg/kg (the highest dose tested; HED of (b) (4) g or (b) (4) the MDE from the drug product) up to 2 years; 2) the excipient has been used as an OTC antacid in Japan and USA with an MDE of (b) (4) mg/day (b) (4) the MDE in the formulation); 3) the excipient has been used in FDA approved drugs products of similar durations up to (b) (4) mg; 4) the acceptable (b) (4) has been used in FDA approved products up to (b) (4) mg for chronic use and at higher levels for drugs approved for shorter durations. While the toxicity data provided by the Applicant was generally limited in that it did not address the full reproductive/developmental endpoints and would not be sufficient alone, the other points considered in the weight of the evidence would address the lack of the full reproductive/developmental including the human experience as an antacid, its use in FDA approved products as magnesium aluminometasilicate (albeit at lower levels), and the higher levels of the acceptable (b) (4) in FDA-approved products.

In the leachable studies, no leachables were detected above the AET in any of the three batches of drug product at 29 months from the date of manufacture.

All impurities are adequately controlled based on the appropriate guidances and do not raise a safety concern from the nonclinical perspective.

Taken together, there are adequate nonclinical data to support the safety of the drug product for the proposed clinical indication. From the nonclinical pharmacology/toxicology perspective, NDA 211759 may be approved.

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

/s/

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07/01/2025 05:15:23 PM

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