CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211759Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	CDR Leah Crisafi, MD, FASA Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine, Office of Neuroscience, CDER, FDA
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	211759/6
Applicant	codaDOSE Inc.
Date of Submission	September 30, 2024
PDUFA Goal Date	July 29, 2025
Proprietary Name	Vyscoxa
Established or Proper Name	Celecoxib oral suspension
Dosage Form(s)	Oral suspension
Applicant Proposed Indication(s)/Population(s)	• For the management of signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) • For the management of signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients 2 years of age and older
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s)	Same as above

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Armaghan Emami, PhD; Jaime D'Agostino, PhD; Jay Chang, PhD
OPQ Review	Valerie Amspacher, PhD
Microbiology Review	Peggy Kriger, PhD
Clinical Pharmacology Review	Wei Qiu, PhD; Deep Kwatra, PhD
OPDP	LaToya Shenee Toombs, PharmD, CPH
OSI	Makini Cobourne-Duval, PhD; Hasan Irier, PhD; Seongeun Cho, PhD
CDTL Review	Robert Shibuya, MD; Tina Doshi, MD, MHS
OSE/DEPI	N/A
OSE/DMEPA	Susan Hakeem, PharmD; Deborah Myers, RPh, MBA; Valerie Vaughan, PharmD; Damon Birkemeier, PharmD, FISMP; Idalia Rychlik, PharmD
OSE/DRISK	N/A
Other	N/A

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Vyscoxa is a celecoxib suspension for oral administration that relies on the findings of safety and efficacy of Celebrex (NDA 020998). The Applicant proposes indications for Vyscoxa where an individual dose may be at or below 200 mg. These indications are for osteoarthritis (OA), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), and ankylosing spondylitis (AS), all of which include an NSAID as first-line pharmacologic treatment for pain caused by the condition. The Applicant has established a scientific bridge to Celebrex by meeting bioequivalence criteria for AUC under fasting conditions with the 200 mg dose.

The benefit of Vyscoxa is that as an oral suspension, it would provide an option for patients who have difficulty swallowing capsules. Celebrex labeling includes the option of sprinkling the capsule contents on a teaspoon of applesauce in Dosage and Administration, Section 2.4 Juvenile Rheumatoid Arthritis. Considering the applesauce method of administration may be easier in concept than in execution, having celecoxib available as a suspension could be of benefit to many pediatric and adult patients.

Safety concerns with the product raised in the CDTL review stem from a substantial food effect. Vyscoxa 200 mg has single-dose $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, of 50%, 35%, and 144%, respectively, higher when taken with a high-fat, high-calorie meal, compared to when taken while fasted. However, this impressive C_{max} value is exaggerated in that the single-dose C_{max} of Vyscoxa in the fasted state is 22% lower than for Celebrex in the fasted state. Compared instead to Celebrex, Vyscoxa 200 mg taken with a high-fat, high-calorie meal has single-dose $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, of 23%, 14%, and 73%, respectively, higher than Celebrex in the fasted state.

I have concluded that the single-dose C_{max} being higher with Vyscoxa than with Celebrex is not a safety concern for several reasons. First is that exposure of a patient to the 73% higher C_{max} would be an isolated occurrence at the beginning of treatment occurring only in those patients who do not follow the instructions not to take the product with food. Second is that the percent to which C_{max} of Vyscoxa exceeds that of Celebrex is expected to be even lower (below 73%) if compared to a single dose of Celebrex administered with food, as is a well-established practice according to the CDTL memo. Third, single-dose C_{max} of 200 mg of Vyscoxa in the fed state would not exceed the C_{max} of Celebrex at the 400 mg dose, which has been concluded to be safe based on approval of 400 mg as an initial dose for a diagnosis of acute pain or primary dysmenorrhea, and as a daily dose for ankylosing spondylitis.

Because Vyscoxa will be used for repeat dosing, the food effect with repeat dosing was evaluated through modeling and simulations. For 200 mg BID dosing for 14 days of Vyscoxa and Celebrex in the fasting state, C_{max} values were 19% lower for Vyscoxa than Celebrex, and the products were bioequivalent for simulated steady state AUC_{0-12}. For 200 mg BID dosing of Vyscoxa and Celebrex in the fed state, C_{max} values were within bioequivalence criteria, and the simulated steady state AUC_{0-12} was approximately 25% higher for Vyscoxa than Celebrex. This leads to the clinical pharmacology recommendation of approval, provided the clinical team is comfortable with the potential for 25% greater steady state AUC values of Vyscoxa and the increase in single-dose C_{max} that was addressed in the previous paragraph.

The CDTL, Dr. Shibuya, recommends Complete Response for this Application. His concern is rooted in the assumption that patients will not adhere to instructions to take Vyscoxa without food and will therefore have a higher celecoxib exposure than intended. He argues that higher exposures would not align with the overarching treatment principle of NSAIDs, to use the lowest effective dose for the shortest possible duration, in order to minimize risk for cardiovascular or gastrointestinal adverse events, and that patients are thereby placed at unacceptable risk if they take Vyscoxa in the fed state.

While it has not been supported by data, Dr. Shibuya could have a valid concern that patients and prescribers may not realize that Vyscoxa is to be taken with food. I also understand his thinking that taking an NSAID without food contradicts common knowledge such that compliance may be low. However, I do not agree with his conclusion that the potential 25% increased exposure in patients who take Vyscoxa with a high-fat, high-calorie meal as a matter of routine despite labeling for the product to be taken without food justifies not approving the product.

Vyscoxa has the benefit of providing an alternative to celecoxib capsules for patients who have difficulty swallowing pills. It has a pronounced food effect, with increased absorption when taken with a high-fat, high-calorie meal. This food effect, however, is not expected to substantially increase the risk of the product as compared to celecoxib capsules at the 200 mg dose or lower based on my overall assessment of risk, noting that dosing instructions for Celebrex are food-agnostic, and taking into consideration the following: (1) the single-dose C_{max} would not exceed that concluded to be safe in other indications, (2) the repeat-dose AUC values in the fed state based on modeling and simulations are not likely to exceed those concluded to be safe based on labeling for AS, acute pain, and primary dysmenorrhea, (3) the food effect is smaller with AUC than with Cmax, with AUC likely to be more relevant to cardiovascular and gastrointestinal risks, (4) the high-fat, high-calorie meal where Vyscoxa has been studied and demonstrated the pronounced food effect is designed to represent one end of the spectrum for maximal detection of food effect. Considering the benefit the product may provide to some patients, labeling is sufficient risk mitigation against the possibility of what is arguably a small increase in exposure over that intended and the potential accompanying risks, and I therefore recommend that Vyscoxa be approved for the conditions of OA, RA, JRA, and AS, for individual doses of up to 200 mg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoarthritis (OA) is a common condition typically presenting as pain in an affected joint. Not all patients with radiographic OA are symptomatic. The incidence is higher in females than males and increases with age while appearing to level off after age 70. • Rheumatoid arthritis (RA) is an autoimmune peripheral polyarthritis with a characteristic distribution of joint involvement. It is twice as common in females as in males. Poor outcomes were common prior to the availability of disease-modifying antirheumatic drugs (DMARDs). • Juvenile rheumatoid arthritis (JRA), also referred to as juvenile idiopathic arthritis, is the most common rheumatologic disease in children. Manifestations are varied, but may include joint pain, stiffness, and swelling, and fever, rash, and uveitis. • Ankylosing spondylitis (AS) is characterized by radiographic sacroiliitis and otherwise has varying disease manifestations such as pain in the neck, back, and other joints, enthesitis, dactylitis, uveitis, inflammatory bowel disease, and psoriasis. Prognosis depends on area and extent of involvement and has improved with the availability of DMARDs.	The four conditions for which this product is proposed can be debilitating diseases. While the understanding of osteoarthritis pathophysiology is evolving, it is distinct from the other indications in that it is a disease and diagnosis that is understood to occur in an individual joint, whereas the other diagnoses are systemic diseases involving multiple organ systems.
Current Treatment Options	• OA management depends on the joint involved but includes many non-pharmacologic treatments or, for severe disease, surgical treatment. First line pharmacological treatments may include oral or topical non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids, and there are numerous second-line treatment options available. • RA first line treatment is DMARD administration. Separately, symptomatic treatment may include NSAIDs, glucocorticoids, or other analgesics (e.g., capsaicin, acetaminophen, tramadol, other opioids). • JRA first line treatment for patients with mild disease is administration of an NSAID. In moderate to severe disease, a DMARD is first-line treatment, with NSAIDs co-prescribed if needed for pain. • AS first line treatment includes non-pharmacologic treatments and administration of an NSAID. Second-line therapy for the minority of patients for whom NSAIDs are not sufficiently effective is a DMARD.	Multimodal treatment is commonly recommended for these four diseases, with NSAID administration being first line pharmacological treatment for the pain component. DMARD administration is first- or second-line treatment in RA, JRA, and AS, and appears to have improved long-term outcomes with these diseases. Celecoxib is one of several NSAIDs that may be prescribed for these conditions, and I note that only in AS is a trial of treatment with two different NSAIDs recommended before moving to a DMARD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Because it is an oral suspension, Vyscoxa would provide an option for patients who have difficulty swallowing capsule presentations of celecoxib that are currently marketed. Examples include pediatric patients with JRA who are too young to swallow capsules, or patients with RA and oropharyngeal or esophageal dysphagia. • The CDTL, Dr. Shibuya, questions the benefit of Vyscoxa, writing that patients who "cannot swallow a solid oral dosage form have the option to sprinkle celecoxib capsules over a semi-liquid food such as applesauce." However, what the labeling states specifically is in Section 2.4, Dosage and Administration for JRA, that "For patients who have difficulty swallowing capsules, the entire contents of a CELEBREX capsule can be…carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested…" In Section 12.3 Pharmacokinetics, it states "In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in Cmax, Tmax, or t1/2…"	The availability of an oral suspension provides another option for patients. It may simplify administration of the first line medication indicated for treatment of pain for patients with each of the four indications. For the adult autoimmune conditions, where patients may have cervical spine, oropharyngeal, or esophageal disease involvement, or for patients with arthritis or other disease manifestations in their hands, the availability of an oral solution may help patients achieve pain control, whereas administration of capsule contents sprinkled on a teaspoon of applesauce, if interpreted as an approved route of administration for these indications, may be easier in concept than in execution. Pediatric patients may also prove reluctant to cooperate with the applesauce technique, with the oral solution potentially being more agreeable.
Risk and Risk Management	• A substantial food effect with Vyscoxa leads to AUC0-t, AUC0-inf, and Cmax of 50%, 35%, and 144%, respectively, higher when taken with a high-fat, high-calorie meal, compared to when taken while fasted. • Vyscoxa taken with a high-fat, high-calorie meal leads to AUC0-t, AUC0-inf, and Cmax of 23%, 14%, and 73%, respectively, higher than with Celebrex capsules taken while fasted. • Modeling and simulations of 200 mg BID dosing under fasted condition for 14 days of Vyscoxa and Celebrex were within bioequivalence criteria for AUC; Vyscoxa was 19% lower for Cmax. • Modeling and simulations of 200 mg BID dosing under fed condition for 14 days of Vyscoxa and Celebrex were within bioequivalence criteria for Cmax; Vyscoxa was 25% higher for AUC. • The PK profile of Vyscoxa when taken with food that would not be classified as "a	Regarding the single-dose exposure that is a 73% higher Cmax (with Vyscoxa with food vs Celebrex while fasted), it would be an isolated occurrence at the beginning of treatment occurring only in those patients who do not follow the instructions not to take the product with food. The percent to which Cmax of Vyscoxa exceeds that of Celebrex is expected to be even lower (below 73%) if compared to a single dose of Celebrex administered with food as is a well-established practice per the CDTL review. Additionally, single-dose Cmax of 200 mg of Vyscoxa in the fed state would not exceed the Cmax of Celebrex at the 400 mg dose, which has been

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	high-fat, high-calorie meal" has not been characterized. • Celebrex has a boxed warning for serious cardiovascular thrombotic events, including myocardial infarction and stroke, which states they may occur early in treatment and may increase with duration of use. • Increased systemic exposure due to taking Vyscoxa with food could increase the risk of serious cardiovascular thrombotic events. • Celebrex has a boxed warning for serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which states they can occur at any time during use and without warning symptoms, with elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding at greater risk. • Celecoxib is a COX-2 inhibitor, for which the risk of GI adverse events would theoretically be lower than for non-selective COX inhibitors. • The CDTL memo describes "well-established prescriber recommendations and patient practice to dose NSAIDs with food to improve gastric tolerability." However, the labeling of NSAIDs does not have such a recommendation in the Dosage and Administration section. Furthermore, taking NSAIDs with food is not mentioned as a risk mitigating strategy in Warnings and Precautions Section 5.2, Gastrointestinal Bleeding, Ulceration, and Perforation. Thus, a linkage between GI adverse events with celecoxib taken while fasting is not made clear.	concluded to be safe based on approval of 400 mg as an initial dose for a diagnosis of acute pain or primary dysmenorrhea, and as a daily dose for ankylosing spondylitis. Therefore, the single-dose Cmax is not a safety concern. Regarding the increased AUC of Vyscoxa vs Celebrex, modeling and simulations with repeat-dose administration of 200 mg BID for 14 days, thus reflecting how the product will be used, demonstrated comparability between the products in AUC when both are taken in the fasting state. With Vyscoxa and Celebrex both in the fed state, bioequivalence criteria were met for Cmax; for AUC, Vyscoxa was 25% higher. The fed state would represent a high-fat, high-calorie meal with every dose (of Vyscoxa or Celebrex), and in the scenario, celecoxib exposure was approximately 25% higher than Celebrex. As this represents a worst-case scenario of a patient who is consistently non-adherent to labeling instructions to take the product while fasting, this degree of increased exposure represents a remote possibility. Additionally, exposures in that case would not exceed those concluded to be safe for other conditions. The standard language regarding using the lowest dose for the shortest duration language applies to this product as to other NSAIDs, and instructions in the labeling, to include a Limitation of Use and the medication guide instructing patients to take the product while fasting, is sufficient to mitigate any risk.

2. Background

Celecoxib is a cyclooxygenase-2 (COX-2)-specific non-steroidal anti-inflammatory drug (NSAID) originally approved in 1998. Celebrex (NDA 20998) is the innovator celecoxib product and has the following four indications for chronic conditions each with different dosing instructions and doses ranging from 50 mg to 400 mg per dose:

- Osteoarthritis (OA) 200 mg once per day or 100 mg twice daily.
- Rheumatoid arthritis (RA) 100 mg to 200 mg twice daily.
- Juvenile rheumatoid arthritis (JRA) 50 mg twice daily in patients 10 kg to 25 kg. 100 mg twice daily inpatients more than 25 kg.
- Ankylosing spondylitis (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.

Celebrex also has indications for acute pain and primary dysmenorrhea with the following dosing:

- 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Celecoxib is also available as an oral solution, Elyxyb (NDA 212157), supplied as bottles containing 120 mg in 4.8 mL. Elyxyb has a sole indication of acute treatment of migraine with or without aura in adults, with a recommended dose of 120 mg taken orally with or without food.

The subject of this NDA (NDA 211759) is an oral suspension of celecoxib, with the trade name Vyscoxa. The NDA was first submitted in 2018 but was not filed due to missing clinical and nonclinical elements. Noted in the filing letter was the need for justification of the proposed labeling given the observation of a food effect with the product. During the subsequent Type A meeting, the Agency recommended that the Applicant reformulate the product so that it is bioequivalent to Celebrex.

This is the first resubmission of NDA 211759, which was received on September 30, 2024, and filed on November 29, 2024. The Applicant reformulated the product, conducted a comparative bioavailability and food effect study 915/22, and is seeking approval with the proposed indications limited those where single doses do not exceed 200 mg, based on demonstration that a single dose of 200 mg celecoxib suspension or Celebrex under fasted condition exhibited comparable AUC values.

3. Product Quality

CMC recommends approval of the product, based on reviews of drug substance, drug product, manufacturing, biopharmaceutics, and labeling. See below for summaries from the subdisciplines, including excerpts from Dr. Valerie Amspacher's review.

Drug substance assessment summary follows:

> *The drug substance CMC information for Celecoxib USP contained in NDA 211759 is cross-referenced to DMF (b) (4) (Celecoxib). DMF (b) (4) was most recently reviewed by Brian Cawrse, PhD on 04/25/2025 in support of NDA 211759 and found to be adequate.*
>
> *A Letter of Authorization is on file with both the Applicant and DMF (b) (4) dated 06/12/2022.*
>
> *DA 211759 sets a retest period of (b) (4) months under long-term storage conditions (b) (4) which is acceptable based on the stability data provided in DMF (b) (4)*

Drug product assessment summary follows:

> *Celecoxib Oral Suspension is an opaque white suspension containing 10 mg/mL of Celecoxib. All the excipients used in the formulation are of compendial grade. Except for magnesium aluminometasilicate, the maximum daily exposures of all the excipients are considered qualified for the oral route of administration. See the non-clinical review for qualification of magnesium aluminometasilicate.*
>
> *The proposed specification is adequate to assure the identity, strength, quality, purity, or potency of the drug product through the proposed shelf-life. The proposed limits for the specified and unspecified impurities meet the ICH Q3B guideline's qualification and identification thresholds respectively. The Applicant has provided a risk assessment for nitrosamine impurities. The drug product is not expected to contain any nitrosamine impurities. Celecoxib does not contain a (b) (4) nor it is expected to contain any impurity (b) (4). As such, it has a low inherent risk for the formation of (b) (4) drug substance related impurities.*
>
> *All the non-compendial analytical methods used for testing the drug product have been adequately validated. Batch data shows that the Applicant can manufacture the drug product in a consistent quality. No impurities were detected in the primary batches.*
>
> *The drug product is packaged in a (b) (4) amber (b) (4) bottle with a child resistant (b) (4) closure. Each bottle contains 16 oz (473 mL) of the oral suspension. The container closure components are suitable for use in contact with food. Extractable study detected several extractables – but at low levels. Only limited leachable data has been provided (data from 29-month time point for two batches, and 17- and 29-month time points for the third batch). No leachable were detected in these batches. The proposed container closure system is suitable for packaging the drug product and it is expected to maintain the quality of the drug product through the proposed shelf-life.*

The Applicant has provided 24-months of long-term and 6-months of accelerated stability data. Except for the variation in particle size distribution at the early time points, no trending was noted. Although the particle size distribution method showed significant variation up to the 6-month time point, it can be attributed to the choice of an inappropriate (b) (4) *A revised method was used from 12-month onwards, which did not show any variation. A shelf-life 36 months may be granted, when stored at controlled room temperature 20°C to 25°C.*

Note 1: The Applicant did not assess the palatability of the formulation in a formal study. Instead, they rely on the informal assessment by R&D personnel who had experience with developing pediatric formulations as well by as sales and marketing individuals. In addition, they rely on the indirect evidence that the subjects in the clinical study did not complain about the taste. This was found acceptable from a risk perspective and the clinical team concurred with this assessment.

Note 2: The Applicant did not provide any powder X-ray data to demonstrate there is no polymorphic change to celecoxib during the drug product manufacturing and storage. Because this is an immediate release formulation, the lack of this data was found acceptable from a risk perspective.

The drug product reviewer, Mariappan Chelliah, also concurs with the Applicant's claim of categorical exclusion per 21 CFR 25.31(a) and that no extraordinary circumstances exist as outlined in 21 CFR 25.21.

The manufacturing assessment summary follows:

Celecoxib Oral Suspension, 10 mg/mL, is a white, opaque, (b) (4) *suspension* (b) (4) (b) (4) *ml* (b) (4) *in a 16 oz* (b) (4) (b) (4) *amber bottle, with an induction-sealed, child resistant* (b) (4) *closure with an* (b) (4) *The drug substance, Celecoxib, is a white or almost white,* (b) (4) *powder, practically insoluble in water, non-hygroscopic, and in the most stable polymorph form* (b) (4) *among the five solid forms the drug substance can exist. '*

The manufacturing process for Celecoxib Oral Suspension, 10 mg/mL, consists of (b) (4) *The firm manufactured three submission batches with the scale of* (b) (4) *L. The intended commercial batches are proposed at the same scale. Mostly, the same set of equipment are to be used for submission batches and commercial, except an* (b) (4) *are proposed to improve* (b) (4)

The drug product manufacturer, drug substance manufacturer, and testing facilities have the experience and adequate inspectional history to support the proposed operations.

The biopharmaceutics assessment summary follows:

1) *Dissolution Method and Acceptance Criterion*

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting the proposed dissolution method and acceptance criterion. A summary of key findings is presented below. Solubility results indicate that the solubility of celecoxib would be too low in the physiologic pH range for a dissolution method to work with adequate sink conditions. Therefore, pH values above the physiologic range were tested.

The Applicant developed an in-house dissolution method: Apparatus 2, 75 RPM, 1000 mL 0.04 M sodium phosphate tribasic, pH adjusted to 11.1 with H3PO4, with an SDS concentration of 0.5%. The discriminating ability of the dissolution method was tested using modified formulations that either had two parameters varied at once, had drastic changes, or involved replacing one excipient with another. A dissolution acceptance criterion of Q (b) (4)% in 45 minutes was proposed, which is adequate.

2) Bridging of Formulations

Only one formulation is listed in the drug product development report that was selected for use in clinical trials. Therefore, bridging of formulations is not necessary.

3) Request for Biowaiver

No request for biowaiver was submitted. There is only one strength.

Recommendation:

From a biopharmaceutics perspective, NDA-211759-ORIG-1 for Vyscoxa (Celecoxib Oral Suspension), 10 mg/mL is deemed adequate and recommended for APPROVAL.

Microbiology assessed the submission as adequate, with the following key points specifically noted in the assessment portions of the CMC review. The USP (b) (4)> testing requirements for (b) (4) products were met and the (b) (4) (b) (4) product. Microbial acceptance criteria adhere to the recommendations in USP <1111> and the exhibit batch results meet the criteria. Lastly, the microbial test methods were verified to be suitable following procedures consistent with those in USP Chapters <60>, <61>, and <62>.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology recommends approval of NDA 211759, and their assessment is detailed in Dr. Armaghan Emami's review. However, three nonclinical issues arose during review of this NDA worth mention.

First is the excipient magnesium aluminometasilicate, that appeared to exceed levels observed in other FDA-approved products based review of the Inactive Ingredient Database. The Applicant therefore provided a risk assessment summarizing the findings across eight non-GLP nonclinical toxicology studies in four species, where significant toxicological findings were reported in only one study, with "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." A NOAEL of 3000 mg/kg derived from this study would provide a (b) (4) fold margin of safety for the maximal daily exposure for this excipient. In addition, the Applicant noted that magnesium aluminometasilicate is in the Over-the-Counter antacid Neusilin approved in the US. In the Pharmacology/Toxicology review, Dr. Emami writes, "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 Over-the-counter (OTC) antacid, and relying on a (b) (4) excipient, which is used in FDA-approved products for a similar duration at higher levels for the proposed route of administration."

Second is a drug product impurity specification for (b) (4) that exceeded ICH Q3B(R2) qualification thresholds. However, during review of the NDA, the Applicant reduced the specification to an acceptable level per ICH Q3B(R2).

Third is leachable data of questionable adequacy for evaluation. Additional data submitted during the review cycle were determined to be adequate and did not contain any leachable compounds above the safety concern threshold.

5. Clinical Pharmacology

The Clinical Pharmacology team reviewed the Study 915/22, a comparative bioavailability study, and recommends approval of this NDA. Refer to Dr. Wei Qiu's review for details. Note the studies 083/17 and 087/17 that are included in Dr. Robert Shibuya's Clinical Team Leader and Associate Director for Therapeutic Review memo (CDTL) were not considered in the Clinical Pharmacology review because they were conducted using an earlier formulation of the drug product. The significance of those studies, however, is that they appear to have prompted reformulation of the product and motivated the Applicant's decision to evaluate only the 200 mg dose of Vyscoxa in their comparative bioavailability studies, having concluded that doses above 200 mg would not be bioequivalent to Celebrex. With regard to doses below 200 mg, Dr. Deep Kwatra shared over email that bioequivalence studies at doses below 200 mg were not required because the PK of celecoxib is dose-proportional up to 200 mg.

Study 915/22 was an open-label, single-dose, three-period, six-sequence, two-treatment crossover design study in healthy volunteers that evaluated single doses of 200 mg Vyscoxa under fasted condition, 200 mg Vyscoxa under a high-fat high-calorie fed condition, and 200 mg Celebrex capsule under fasted condition. For Vyscoxa compared to Celebrex, both under fasted condition, the study demonstrated equivalent AUC values and 22% lower Cmax for Vyscoxa. For Vyscoxa under fed condition compared to Celebrex under fasted condition, AUC_{0-t}, AUC_{0-inf}, and Cmax were 23%, 14%, and 73%, respectively, higher with Vyscoxa. PK modeling and simulation was also performed to predict concentration-time profiles with 200 mg BID dosing under fasting condition. Dr. Qiu's review states, "Based on the steady state PK modeling and simulation, the simulated steady state AUC_{0-12} values following 200 mg BID dosing for celecoxib oral suspension were equivalent to Celebrex capsules under fasting condition because the ratio of geometric means and 90% CI were contained within 80% to

125% bioequivalence criteria. The simulated steady state C_{max} values for celecoxib oral suspension were 19% lower." Dr. Qiu's review notes that the lower Cmax is not relevant because the Applicant is seeking approval for chronic pain conditions where efficacy is based on AUC.

Dr. Qiu's review supports approval of Vyscoxa, stating, "From a clinical pharmacology perspective, the information submitted in the NDA resubmission is acceptable (though significant labeling changes are needed) pending [Office of Study Integrity and Surveillance] inspection and assessment on the comparative bioavailability study 915/22." However, the review also acknowledges the potential for higher-than-intended exposure if Vyscoxa is taken with food, stating, "…the proposed celecoxib oral suspension should not be given with food unless there are clinical data to support the safety of celecoxib oral suspension under fed conditions (see Clinical review). We ultimately defer to clinical team regarding whether there will be safety issues associated with increased exposures for patients initiating dosing with this product and the potentially 25% greater steady state AUC for oral suspension."

Of note, the Office of Study Integrity and Surveillance review was finalized on July 18, 2025, and Dr. Makini Cobourne-Duval writes, "After reviewing the inspectional findings, exhibits provided in the [Establishment Inspection Report], and the firm's response to the discussion items per the [Establishment Inspection Report], there are no concerns regarding the reliability of the data of human subject protection for inspected study 915/22."

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

In this new drug application, the Applicant has provided the substantial evidence of effectiveness required by law 21 CFR 314.126(a)(b) to support approval. The application relies on the Agency's finding of safety and effectiveness of Celebrex, NDA 20998, as the listed drug. The Applicant has established a scientific bridge by meeting bioequivalence criteria for AUC under fasting conditions with the 200 mg dose, and therefore, effectiveness of Vyscoxa has been established for only those indications where an individual dose may be at or below 200 mg. These indications are osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. Excluded are Celebrex's indications for acute pain and primary dysmenorrhea, where the starting dose is 400 mg.

8. Safety

As stated above, this application relies on the Agency's finding of safety and effectiveness of Celebrex, NDA 20998, as the listed drug. The Applicant has established a scientific bridge by meeting bioequivalence criteria for AUC under fasting conditions with the 200 mg dose.

A single 200 mg dose of Vyscoxa taken with a high-fat, high-calorie meal, yields AUC_{0-t}, AUC_{0-inf}, and C_{max} of 50%, 35%, and 144%, respectively, higher than when taken while fasted. These values are helpful for demonstrating the extent of the food effect. However, a comparison to Celebrex is more informative of the extent to which the safety of Vyscoxa is supported by the clinical experience with Celebrex. Compared to Celebrex capsules taken in the fasted condition, Vyscoxa taken with a high-fat, high calorie meal, yields lesser increases in single dose AUC_{0-t}, AUC_{0-inf}, and $C_{max,}$ of 23%, 14%, and 73%, respectively.

Because Vyscoxa is intended to be used for repeat administration (every 12 or 24 hours), I evaluated modeling and simulation results for exposure levels with repeat administration to help determine whether existing experience with Celebrex would support the safety of Vyscoxa. PK modeling and simulation for 200 mg BID dosing of Vyscoxa and Celebrex for 14 days found the ratio of geometric means and 90% confidence interval for AUC_{0-12} within bioequivalence criteria under the fasted condition. Modeling and simulation were also conducted with 200 mg BID dosing for 14 days with Celebrex or Vyscoxa under fed condition, and the simulated steady state AUC_{0-12} for celecoxib oral suspension under was 25% greater than that for Celebrex capsule, while Cmax was comparable. This means that if patients take Vyscoxa with a high-fat, high-calorie meal with each dose, on average their celecoxib exposure would be expected to be 25% higher than if they were taking Celebrex, which is food agnostic, with a high-fat, high-calorie meal. Exposures in this case would not exceed exposures associated with higher doses that have been concluded to be safe and included in labeling.

Safety data from the 54 healthy volunteers enrolled in study 915/22 did not raise any safety concerns with the formulation.

9. Advisory Committee Meeting

This product was not discussed at Advisory Committee.

10. Pediatrics

The Applicant had an Agreed initial Pediatric Study Plan, that included a partial waiver for JRA based on JRA being an approved indication for the Reference Listed Drug for pediatric patients ≥ 2 years of age, and a full waiver for all other indications.

The Application was discussed at the Pediatric Review Committee, including whether studies in JRA should be required. The Division of Rheumatology and Transplant Medicine had previously advised that in the case of bioequivalence, safety and efficacy could be extrapolated from Celebrex and pediatric studies could be waived. The Pediatric Review Committee agreed with granting a full waiver for the OA, RA, and AS indications, and a partial wavier for pediatric patients from birth to < 2 years of age.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

The labeling proposed by the Applicant omits the acute indications and the option to dose administer 400 mg daily for patients with AS but otherwise largely parallels the labeling of the RLD.

To minimize the potential for patients to take Vyscoxa with food, a Limitation of Use was added, stated Vyscoxa must be taken on an empty stomach and should be discontinued in the event of intolerance of the product taken in the fasted state. This and other labeling changes requested by the Agency are summarized in the table below, excerpted from Dr. Shibuya's CDTL memo.

Original	July 2025 FDA Markup	Rationale
Section 1: Limitation of Use was limited (b) (4)	Added "VYSCOXA must be administered on an empty stomach at least 2 hours before or 1 hour after food. Taking VYSCOXA with food results in plasma exposures of celecoxib up to 50% higher than intended. If patients cannot tolerate VYSCOXA in the fasted state, discontinue use of VYSCOXA (reference Sections 12, 2.1, 5).	Risk mitigation for PK mismatch in the fed state
Section 2: No description of recommendation to take on an empty stomach.	Added, "VYSCOXA must be taken on an empty stomach at least 2 hours before or 1 hour after food [see Clinical Pharmacology (12.3)].	Risk mitigation for PK mismatch in the fed state
Sections 6 and 14: (b) (4)	Generally addressed by substituting "VYSCOXA" with "another formulation of celecoxib".	Clarity
Section 12:	In conjunction with the Clinical Pharmacology team, the original language was edited.	Clarity

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/s/

LEAH H CRISAFI
07/29/2025 05:54:26 PM

Clinical Team Leader and Associate Director for Therapeutic Review Memo

Date	See electronic signatures
From	Robert Shibuya, MD, Clinical Team Leader Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Tina Doshi, MD, MHS, Associate Director for Therapeutic Review, DAAP
Subject	Cross-Discipline Team Leader Review and Associate Director for Therapeutic Review Joint Memo
NDA	211759
Applicant	codaDOSE
Date of Submission	July 30, 2024
PDUFA Goal Date	July 29, 2025
Proprietary Name	Vyscoxa
Established or Proper Name	Celecoxib oral suspension
Dosage Form(s)	Oral suspension
Applicant Proposed Indication(s)/Population(s)	Treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis
Applicant Proposed Dosing Regimen(s)	100 to 400 mg/day total dose, once-a-day or twice-a-day (400 mg would be delivered as 200 mg BID)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended Dosing Regimen(s) (if applicable)	Not applicable

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Non-steroidal anti-inflammatory drugs (NSAIDs) represent a medically necessary, widely used group of drugs marketed since acetylsalicytic acid in the 19th century. NSAIDs are approved for a panoply of indications (prescription and over-the-counter), including common painful conditions such as osteoarthritis and acute pain, to narrower indications such as closure of a patent ductus arteriosis. The risks of NSAIDs are well-characterized, with the key risks being cardiovascular adverse events, gastrointestinal bleeding, and renovascular effects. The risks of NSAIDs have been reviewed extensively since the start of the 21st century and are known to be related to dose and duration of treatment. NSAID labeling contains class warnings, including a statement to, "Use the lowest effective dosage for the shortest duration consistent with individual treatment goals."

The subject of this NDA is a celecoxib-containing oral suspension (proprietary name Vyscoxa). Celecoxib is an NSAID with specificity for the cyclo-oxygenase-2 enzyme. Celecoxib has been shown to have lower risks for gastrointestinal adverse reactions compared to non-selective NSAIDs, although the risks of cardiovascular and renovascular adverse events are similar to other NSAIDs.

The medical utility of this new formulation of celecoxib is unclear. Celebrex (celecoxib capsules [NDA 020998]) can be opened and the contents scattered on applesauce for patients who cannot use a solid oral dosage form. The Orange Book shows a large number of generic equivalents to Celebrex.

Clinical data on this product are limited to three comparative bioavailability studies in healthy volunteers (HV). Two studies dosed healthy volunteers with a single dose of 400 mg of Vyscoxa or Celebrex (highest labeled dose for Celebrex). These studies showed that the Vyscoxa had significantly higher celecoxib exposures than the comparator (Celebrex®). Exposures were higher when both products were compared in the fasted state and exposures were higher for Vyscoxa in the fed state compared to fasted. After the single-dose phase 1 studies at 400 mg, the Applicant (b) (4) completed a single-dose study at 200 mg. This study showed comparable exposures to Celebrex in the fasted state, although there was still a pronounced food effect (35% to 50% higher for AUC and >100% higher for Cmax).

The Applicant proposes to market Vyscoxa for the same indications approved in Celebrex, minus the acute pain indications, which specify 400 mg dosing. Risks outweigh the benefits for celecoxib oral suspension (Vyscoxa) for the following reasons:

1. NSAID-related risks are correlated to dose and duration. NSAID class labeling aligns with these known risks and recommends use of the lowest dose for the shortest duration.
2. In the fasted state, 200 mg of Vyscoxa approximates a 200 mg capsule of Celebrex.
    a. If administered in the fasted state, starting at an undefined dose between 200 mg and 400 mg (which is the maximum approved dose for Celebrex), systemic exposures exceed those concluded to be safe and effective for any of the indications proposed by the Applicant.
    b. If administered in the fed state, 200 mg of Vyscoxa delivers 35% to 50% more celecoxib (AUC) than 200 mg of Celebrex.

3. Given 2b, the Applicant has not proposed to add labeling that Vyscoxa must be dosed on an empty stomach, which would be necessary to ensure that the product does not significantly exceed exposures of the reference drug at the same dose. However, that direction would contradict well-established prescriber recommendations and patient practice to dose NSAIDs with food to improve gastric tolerability.
4. Given #3, it is predictable that patients will dose Vyscoxa after a meal, increasing celecoxib exposure beyond the established safe and effective dose for the proposed indications. That is not consistent with prudent NSAID prescription, nor is it consistent with the established safe and effective dose in the relevant patient populations.
5. The patient population with dysphagia would be most likely to benefit from an oral suspension of celecoxib over the existing capsule form. However, these same patients are more likely to be older and have co-morbid conditions that place them at greater risk of harm from celecoxib overdose. It is also important to note that patients who require celecoxib and cannot swallow a solid oral dosage form have the option to sprinkle celecoxib capsules over a semi-liquid food such as applesauce.

Given #1 through #5, the risks of Vyscoxa exceed its implied benefits. The benefits of celecoxib therapy can be achieved through approved products, and Vyscoxa poses a unique risk whose mitigation is not consistent with NSAID administration paradigms.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The indications sought by this Applicant are osteoarthritis (OA), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), and ankylosing spondylitis (AS). • The proposed labeling includes a Limitation of Use stating that acute pain and primary dysmenorrhea are not indicated for this product although they are approved indications for Celebrex.	Due to issues identified during development (exposure mismatch for a 400 mg loading dose/paucity of data in women), the Applicant is only seeking indications for chronic pain conditions and not acute pain or primary dysmenorrhea.
Current Treatment Options	• The listed drug (Celebrex) encompasses all indications proposed.	The only theoretical advantage attributable to Vyscoxa is that it is not a solid oral dosage form and could be useful in patients with dysphagia and/or who cannot or will not use solid oral dosage forms.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Celebrex capsules can be broken open and the contents sprinkled into applesauce. Theoretically, Elyxyb (celecoxib oral solution [NDA 212157]), approved for acute treatment of migraine, could also be used off-label in such patients.
Benefit	• This Applicant is relying on exposure matching from three studies conducted in healthy volunteers to extrapolate efficacy and safety from Celebrex.	The AUC for Vyscoxa in the fasted state at a 200 mg dose approximates Celebrex and could be considered bioequivalent for AUC. The Cmax at 200 mg in the fasted state is 78%, below the bioequivalence standard. However, given the known pharmacodynamics of celecoxib and the fact that the proposed indications are for chronic conditions, that excursion is not clinically significant.
Risk and Risk Management	• Exposures at a 400 mg dose of Vyscoxa show Cmax and AUC substantially greater than 400 mg of Celebrex. • The food-effect study at 200 mg shows large effects on AUC (~35 to 50% higher) and Cmax (~100% higher) in the fed state where Vyscoxa > Celebrex.	I considered labeling this product for use only in the fasted state, where the exposures for the oral suspension approximate Celebrex capsule at 200 mg. However, that would be contrary to most recommendations, which are to take NSAIDs with food to improve tolerability. Assuming less than 100% compliance with labeled dosing recommendations, especially likely considering their divergence from well-established clinical practice, some patients will have significantly higher exposures than intended. Given the class labeling to use the lowest dose for the shortest duration to mitigate the cardiovascular and gastrointestinal (GI) risks, knowing that some patients will be overdosed is not acceptable. I note that Xtampza (NDA 208090)* was approved despite a pronounced food effect. Xtampza is an extended-release formulation of oxycodone with purported "abuse-deterrent" properties. The food effect studies for Xtampza showed increases in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Cmax of 100% to 150% and increases in AUC of 50% to 60% after a high-fat meal. This finding was addressed by instructing patients to take Xtampza with food (Section 2.1 of the package insert) which accounts for the food effect. Patient noncompliance would result in exposures less than expected, which does not represent a safety issue. Vyscoxa represents the converse situation. If patients are not compliant with directions to take on an empty stomach, they will unintentionally overdose. This may declare itself with transient GI symptoms such as dyspepsia. However, unlike an opioid, higher than intended NSAID exposure will likely not be detectable and risks will be cumulative if the dosing error is not corrected. Additional information about potentially relevant approved products is in the APPENDIX to this document.

*See Appendix #

2. Background and Pertinent Regulatory History

The subject of this review is an oral suspension of celecoxib (conditional tradename - Vyscoxa). Celecoxib is a cyclo-oxygenase 2 (COX-2)-specific inhibitor, a subset of the nonsteroidal anti-inflammatory drug (NSAID) class. The first approved celecoxib-containing drug was Celebrex (NDA 020998), initially approved in 1998. Celebrex is a capsule approved for osteoarthritis (OA), rheumatoid arthritis (RA), "Juvenile Rheumatoid Arthritis" (JRA) in patients 2 years and older, ankylosing spondylitis (AS), acute pain (AP), and primary dysmenorrhea (PD). Other approved celecoxib-containing products are summarized below:

Product/NDA number/Formulation	Indication
Celebrex®/020998/capsule	Multiple, as above
Elyxyb/212157/oral solution	Acute migraine, with or without aura
Consensi/210045/tablet (fixed combination with amlodipine)	OA and hypertension
Seglentis/213426/tablet (fixed combination with tramadol)	Opioid acute pain indication

A New Drug Application (NDA) for Vyscoxa was submitted on March 9, 2018. The Agency issued a "Refuse To File" (RTF) action on April 30, 2018, citing the following clinical and nonclinical deficiencies.

Clinical

1. The submission lacks an integrated summary of safety (ISS), integrated summary of efficacy (ISE), and a benefit-risk analysis for the product. These sections are required for an NDA submission. Provide these sections. You may cross-reference the clinical summaries of efficacy and safety in Module 2 if these sections contain adequate information.
2. The clinical section is not legible and organized in a manner to allow substantive review. For example, some of the tables in Module 2.7.1 are unclear as there are dashes rather than numbers which appear to indicate that there are no events. Provide the data in an organized manner to allow substantive review. In addition, all documents must be in their final version without track changes.
3. The documents entitled "Summary of Results of Individual Studies" in Module 2 are not consistent with the required discipline summaries since they only include information from individual studies. In addition, these summaries only include tables. Provide the required discipline summaries and provide the information in a manner to allow substantive review.
4. There is no discussion of the relevance of the information intended to provide the scientific bridge between your product and the referenced materials. Provide information to support the relationship between the proposed product and the listed drug/published literature, including a discussion of the comparative bioavailability results (i.e., 51% greater Cmax and 20% greater AUCs for the proposed oral suspension than Celebrex capsule).
   Given that the product was not bioequivalent to the listed drug, include a description of how this impacts considerations related to efficacy and safety of the proposed product.

Given that the product shows an increase in relative systemic exposure compared to the listed product, provide additional information to support the safety of the proposed product. Include copies of all referenced citations in the NDA submission. Translate all journal articles that are not in English into English.

5. There is no safety assessment based on all current worldwide knowledge regarding celecoxib. Provide this information.
6. There is no evaluation of the safety issues that are known to occur with the drugs in the class to which the proposed drug belongs. Provide this information.
7. The proposed pediatric assessment fails to discuss the lack of bioequivalence between the proposed product and listed drug. Submit a discussion of how the increased exposure impacts the proposed pediatric plan.
8. There is no review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) and update the labeling to be compliant with the Pregnancy and Lactation Labeling Rule (PLLR). Provide this information.
9. If foreign data are submitted, provide a rationale for assuming the applicability of foreign data in the submission to the U.S. population.
10. The two submitted clinical pharmacology trials only included male subjects and there is no discussion of how these data are appropriate to support an indication of primary dysmenorrhea. Provide a rationale to explain how the pharmacokinetic data of South Asian males would be applicable to U.S. premenopausal females. Such an explanation may include information to demonstrate that the pharmacokinetic profile of the South Asian men is comparable to that of premenopausal women in the U.S. Alternatively, conduct new bridging PK studies in premenopausal women in the U.S.
11. To establish the safety of the proposed oral suspension for the primary dysmenorrhea indication, provide the following:
    a. A summary and analysis of published literature, including copies of individual publications, to support the safety of the new formulation. If available, include all published literature assessing celecoxib for primary dysmenorrhea at doses greater than 400 mg.
    b. A summary and analysis of post-marketing pharmacovigilance data such as line listing data in the FDA's Adverse Events Reporting System (FAERS).
    c. A summary of safety data for the completed clinical pharmacology trials.

Nonclinical

12. The application does not contain a Nonclinical Module 2 and Module 4 and is lacking pharmacology and toxicology information to allow for a substantive review.
    a. Submit nonclinical information that is organized in accordance with current regulations and guidelines for eCTD content and format.
    b. Submit Module 2.6 Nonclinical Written and Tabulated Summaries based on the referenced drug product and a review of the literature since approval of the referenced drug product. Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of the

proposed drug product. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.

c. In Module 2 of the application (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

13. The nonclinical sections in the submitted label are not consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). To comply with PLLR content and format requirements, conduct a thorough review and of the available published nonclinical literature on animal reproductive and developmental toxicology studies with celecoxib and provide a summary of these studies along with an integrated summary to inform Sections 8 and 13 of the label. Information on the final rule and links to the FDA draft guidance document are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

Type A Meeting: June 29, 2018

Key clinical agreements and comments follow:

1. Reiterated that ISS/ISE and B-R analysis are required.
2. The discussion of the clinical implications of the exposure mismatch was not acceptable as described in the Meeting Package. The Sponsor proposed to label to "provide comparable systemic exposure." There was discussion of lowering the nominal dose with no resolution.
3. The fact that the studies were conducted in ex-US populations is mitigated by the cross-over design. However, the exposure mismatch will still require addressing.
4. The Agency recommended that the Applicant reformulate to mitigate the food effect. We note that, in the current submission, the Applicant states that they reformulated although the new formulation still has the pronounced food effect.

APPLICANT'S COMPLETE RESPONSE

The Applicant's responses to the RTF deficiencies are summarized in Table 1, below.

Table 1: RTF clinical deficiencies and Applicant's responses

Deficiency (paraphrased)	Response (paraphrased)	Comment
No ISS/ISE and B-R analysis	Submission contains these sections.	Acceptable
Legibility and organization	Current submission is acceptable.	Acceptable
Compliance with requirements for discipline summaries	Current submission is acceptable.	Acceptable

No discussion of the impact of the exposure mismatch	The Applicant has abandoned the acute pain indications (AP and PD) that permit a single 400 mg loading dose. Therefore, the Applicant asserts the mismatch at 400 mg is irrelevant. Regarding the 200 mg dose, the Applicant argues that Vyscoxa and Celebrex® are bioequivalent. The proposed package insert indicates that Vyscoxa can be taken with or without food (Section 2.1).	Not acceptable. See Benefit-Risk Assessment and Clinical Pharmacology sections for details.
No safety summary of worldwide safety information for drug class	Submitted in response to Information Request.	Acceptable
Pediatric assessment fails to discuss exposure mismatch	This item is effectively moot because pediatric studies in JRA were waived per an agreed iPSP dated January 22, 2024.	N/A
No review of available information in pregnant, lactating women, and females and males of reproductive potential	Nominally addressed	Will be reviewed by DMPH and P/T.
Provide rationale for applicability of foreign data	Adequately addressed.	Acceptable
Discuss how phase 1 studies in men apply to the primary dysmenorrhea indication	Revisions to Indications have rendered this deficiency not applicable.	N/A
Submit additional information around the primary dysmenorrhea indication	Revisions to Indications have rendered this deficiency not applicable.	N/A

3. Product Quality

No product quality deficiencies were identified in the Refuse to File (RTF) Letter. The Office of Product Quality (OPQ) team conducted a review of the Application. OPQ noted the change in the excipient (magnesium aluminometasilicate) described in greater detail in the Pharmacology/Toxicology (P/T) review. OPQ has recommended approval of this product.

4. Nonclinical Pharmacology/Toxicology

The RTF Letter contained two deficiencies pertaining to failure to submit two eCTD modules and draft labeling not in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). The P/T review also notes that, in the interval between the RTF Action and the current submission, the Applicant reformulated the drug product with the goal of meeting bioequivalence criteria. The excipient (magnesium aluminometasilicate (MASM), was reviewed by our P/T team and I was asked for clinical comments. MASM is contained in FDA-approved products although the exact spelling of the molecule varies slightly.

I reviewed relevant sections of the submission and downloaded the product labeling for the approved OTC antacid. The doses from the literature and potentially used as an antacid are

much higher than that delivered in maximum doses of Vyscoxa. The antacid labeling allows up to 2 bottles, each containing 900 mg of the molecule/day (compared to 200 mg/day in the celecoxib product).

There is no direct support for the MASM in Vyscoxa from the perspective of chronicity. The longest study referenced by the Applicant dosed for 30 days. The antacid labeling notes not to use for >2 weeks but I assume that is to prompt the patient to seek medical advice after a trial of the OTC antacid. However, I am inclined to accept the human experience to support inclusion at 200 mg/day in Vyscoxa. The dose is not very high, the drug is not absorbed and there are likely decades of use in patients who might not abide by the 2-week restriction. After their thorough review, the P/T accepted the Applicant's weight-of-evidence argument for MASM. P/T has recommended Approval of Vyscoxa.

5. Clinical Pharmacology

Please see Dr. Wei Qiu's review for additional details regarding the completed clinical pharmacology studies.

The Applicant has completed three comparative bioavailability studies conducted in healthy volunteers (HV) and asserts that these studies support approval under the 505(b)(2) approval mechanism. The studies were all of an open-label, single-dose, crossover design. A high-level summary of the studies submitted (Table 2) follows, followed by a discussion by study.

Table 2: High-level summary of completed comparative bioavailability studies

<table>
<tr><th>Study #</th><th></th><th>Treatments</th><th>Key Findings</th></tr>
<tr><td>083/17</td><td>•</td><td>• Vyscoxa 400 mg (40 mL x 10 mg/mL) - FASTED
• Celebrex 400 mg capsule – FASTED
• Used an earlier formulation of the drug product</td><td>Demographic: All men

Pharmacokinetic (PK)
<table>
<tr><th></th><th colspan="2">Arithmetic Mean ± SD (N = 45)</th></tr>
<tr><th></th><th>Test product (T)</th><th>Reference product (R)</th></tr>
<tr><td>#T_{max} (hr)</td><td>1.500 (1.000 – 4.330)</td><td>2.670 (1.000 – 4.670)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>1577.6073 ± 576.54650</td><td>1034.2624 ± 352.01055</td></tr>
<tr><td>AUC_{0-t} (hr*ng/mL)</td><td>14865.5819 ± 5737.15954</td><td>12364.7649 ± 5029.13376</td></tr>
<tr><td>AUC_{0-inf} (hr*ng/mL)</td><td>15202.4749 ± 5821.74355</td><td>12739.9549 ± 5105.12268</td></tr>
<tr><td>$t_{1/2}$ (hr)</td><td>8.7999 ± 2.47508</td><td>8.8981 ± 2.46381</td></tr>
<tr><td>K_{el} (1/hr)</td><td>0.0848 ± 0.02280</td><td>0.0842 ± 0.02448</td></tr>
</table></td></tr>
<tr><td>087/17</td><td>•</td><td>• Vyscoxa 400 mg (40 mL x 10 mg/mL) - FASTED
• Vyscoxa 400 mg (40 mL x 10 mg/mL) - FED
• Used an earlier formulation of the drug product</td><td>Demographic: All men

Pharmacokinetic (PK)
<table>
<tr><th></th><th colspan="2">Arithmetic Mean ± SD (N = 18)</th></tr>
<tr><th></th><th>Test in Fed (Fe)</th><th>Test in Fasting (Fa)</th></tr>
<tr><td>#T_{max} (hr)</td><td>3.165 (1.000 - 4.670)</td><td>2.000 (1.000 - 3.670)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>2675.2371 ± 795.53299</td><td>1594.5859 ± 700.81702</td></tr>
<tr><td>AUC_{0-t} (hr*ng/mL)</td><td>26501.5430 ± 11515.40290</td><td>17188.4067 ± 8557.95086</td></tr>
<tr><td>AUC_{0-inf} (hr*ng/mL)</td><td>26889.7526 ± 11825.13376</td><td>17591.2169 ± 8596.31958</td></tr>
<tr><td>T_{lag} (hr)</td><td>0.0000 ± 0.00000</td><td>0.0000 ± 0.00000</td></tr>
<tr><td>$t_{1/2}$ (hr)</td><td>8.2052 ± 2.62556</td><td>8.9698 ± 3.66239</td></tr>
<tr><td>K_{el} (1/hr)</td><td>0.0917 ± 0.02511</td><td>0.0873 ± 0.02849</td></tr>
<tr><td>$AUC\_{}_{\%Extrap-obs}$ (%)</td><td>1.3128 ± 1.05111</td><td>2.9234 ± 5.11853</td></tr>
</table></td></tr>
<tr><td>922/15</td><td>•</td><td>• Vyscoxa 200 mg (20 mL x 10 mg/mL) - FASTED</td><td>Demographic: 25 female, 29 male

Pharmacokinetic (PK)</td></tr>
</table>

		• Vyscoxa 200 mg (20 mL x 10 mg/mL) - FED • Celebrex® 200 mg capsule – FASTED	**Summary Table of the Bioequivalence Data of Celecoxib** <table><tr><th rowspan="2">Parameter</th><th colspan="4">GEOMETRIC LEAST SQUARES MEANS</th><th rowspan="2">RATIO T_{FA}/R_{FA} (%)</th><th colspan="2">90% CONFIDENCE LIMITS (%)</th><th rowspan="2">BE</th><th rowspan="2">CV_{intra} (%)</th></tr><tr><th>N</th><th>T_{FA}</th><th>N</th><th>R_{FA}</th><th>Lower</th><th>Upper</th></tr><tr><td>$AUC_{(0-t)}$ (ng·h/mL)</td><td>51</td><td>3932.2</td><td>51</td><td>4281.5</td><td>91.84</td><td>86.79</td><td>97.19</td><td>YES</td><td>17.15</td></tr><tr><td>$AUC_{(0-\infty)}$ (ng·h/mL)</td><td>51</td><td>4512.7</td><td>51</td><td>4784.3</td><td>94.32</td><td>89.50</td><td>99.40</td><td>YES</td><td>15.89</td></tr><tr><td>C_{max} (ng/mL)</td><td>51</td><td>324.2</td><td>51</td><td>416.1</td><td>77.92</td><td>71.08</td><td>85.41</td><td>NO</td><td>28.15</td></tr></table>N = Number of Observations **Summary Table of the Food Effect Data** <table><tr><th rowspan="2">Parameter</th><th colspan="4">GEOMETRIC LEAST SQUARES MEANS</th><th rowspan="2">RATIO T_{FE}/T_{FA} (%)</th><th colspan="2">90% CONFIDENCE LIMITS (%)</th><th rowspan="2">Food Effect</th><th rowspan="2">CV_{intra} (%)</th></tr><tr><th>N</th><th>T_{FE}</th><th>N</th><th>T_{FA}</th><th>Lower</th><th>Upper</th></tr><tr><td>$AUC_{(0-t)}$ (ng·h/mL)</td><td>52</td><td>5834.9</td><td>52</td><td>3899.2</td><td>149.64</td><td>139.58</td><td>160.44</td><td>YES</td><td>21.41</td></tr><tr><td>$AUC_{(0-\infty)}$ (ng·h/mL)</td><td>52</td><td>6048.8</td><td>52</td><td>4481.9</td><td>134.96</td><td>125.94</td><td>144.63</td><td>YES</td><td>21.27</td></tr><tr><td>C_{max} (ng/mL)</td><td>52</td><td>791.3</td><td>52</td><td>323.8</td><td>244.36</td><td>224.42</td><td>266.08</td><td>YES</td><td>26.33</td></tr></table>N = Number of Observations

Table 2 shows:

1. Ata dose of 400 mg (earlier formulation):
    - Vyscoxa has significantly higher exposures compared to a 400 mg dose of Celebrex in the fasted state (~34% Cmax and ~17% AUC).
    - Vyscoxa has a pronounced food effect with ~40% higher Cmax and ~35% higher AUC in the fed state compared to the fasted state.
2. At a dose of 200 mg:
    - In the fasted state, Vyscoxa approximates Celebrex for AUC and has a T_{FA}/R_{FA} ratio of 0.78 for Cmax. Given the exposure-response relationship for NSAIDs, the slight mismatch for Cmax is not clinically significant.
    - The fed state demonstrates a large food effect, whereby exposures were 35% to 50% higher for AUC and >100% higher for Cmax in the fed state compared to the fasted state.

Due to the exposure mismatch at 400 mg, the Applicant abandoned the acute pain indication (requires a 400 mg loading dose) and the primary dysmenorrhea indication (requirements for 400 mg loading dose and adequate data in females).

The clinical and analytical sites that conducted Study 922/15 were inspected. No significant violations were found and the data from the site were deemed acceptable for review. The Applicant also submitted a Form FDA 3454 (Financial Interests) that indicates no conflicts for Dr. Petr Budera, the investigator for Study 922/15 (Czech Republic).

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

CodaDOSE has conducted no studies to assess effectiveness, proposing to leverage the Agency's findings of efficacy for Celebrex using the 505(b)(2) approval mechanism. While data with Vyscoxa are limited, the comparative bioavailability studies show comparable exposures to 200 mg of Celebrex in the fasted state. I note that the exposures in the fasted state at the single dose of 400 mg showed significantly higher exposures for Vyscoxa compared to Celebrex.

The dose at which Vyscoxa becomes significantly more bioavailable in the fasted state is not known. There is a significant mismatch at 400 mg but not at 200 mg. Given that the Applicant has abandoned the acute pain indications (400 mg loading dose), from a strict regulatory perspective, the Applicant has met the requirement for efficacy.

8. Safety

Safety data for Vyscoxa is limited to three open-label, single-dose Phase 1 studies in healthy volunteers. Summaries of the studies and safety data follow:

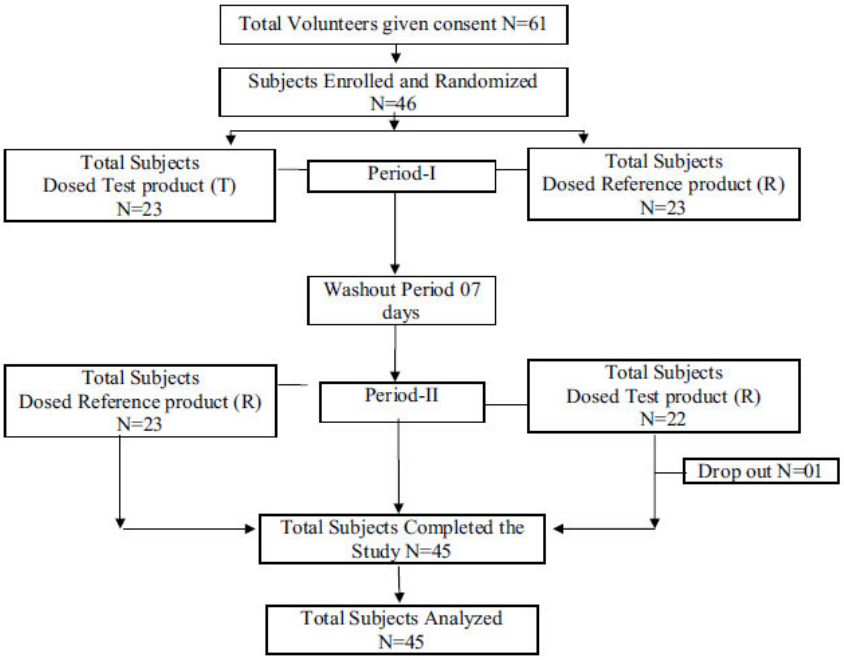
Study 083/17
Objective: Oral bioavailability of Vyscoxa vs. Celebrex at 400 mg, fasted
Design:

- Randomized, open-label, two-treatment, two-period cross-over, single-dose
- Inpatient from Day -1 to 48 hours post dose each period
- At least 7 days washout between periods

Population: Healthy volunteers in India (all male)
N: 46
Monitoring:

- Adverse events – per visit
- Hematology, chemistry, serology, urinalysis at screening and end-of-study
- Vital signs – frequently after each dose, then periodically
- ECG screening and at last PK sampling
- Physical exam at screening and each inpatient check-in

Disposition:



Source: CSR Study 083/17, Table 11

Major Safety Findings:
The CSR states that there were no major safety findings (deaths, non-fatal serious adverse events, or adverse events leading to discontinuation).

Common Adverse Events:
Regarding common adverse events, the CSR states:

12.2.3 Analysis of Adverse Events

All the subjects were monitored for the safety and wellbeing during entire duration of the study.

No adverse events were observed during in-house of the study.

No adverse events were reported in during post study evaluation.

Comments: There were no significant findings for the labs or vital signs. Overall, the safety findings are typical for a Phase 1 study in healthy volunteers and did not reveal formulation-specific concerns.

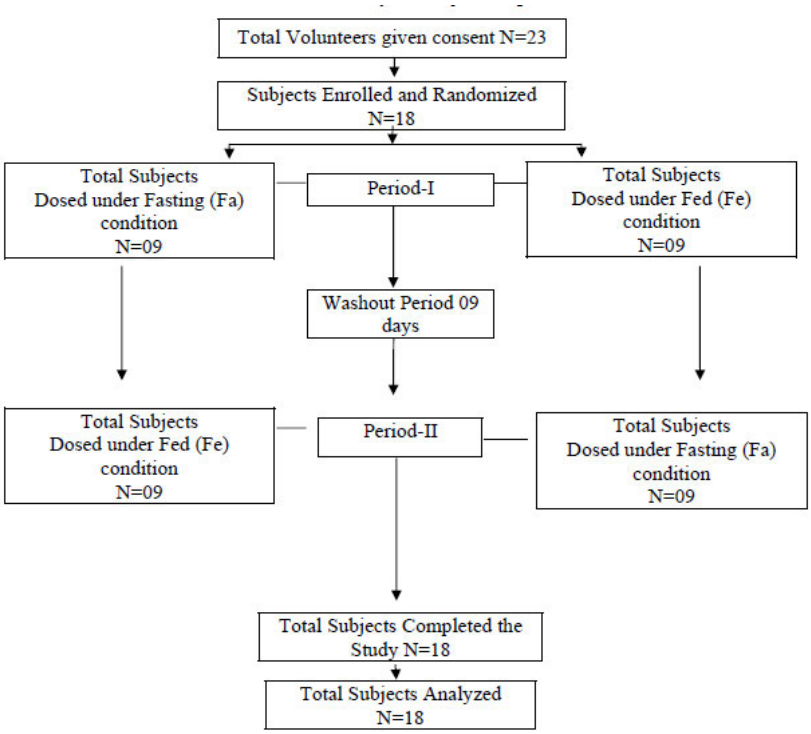
Study 087/17
Objective: Food effect of Vyscoxa vs. Celebrex at 400 mg
Design:

- Randomized, open-label, two-treatment, two-period cross-over, single-dose
- Inpatient from Day -1 to 48 hours post dose each period
- At least 7 days washout between periods

Population: Healthy volunteers in India
N: 18 (all male)
Monitoring:

- Adverse events – per visit
- Laboratory monitoring was not required per protocol
- Vital signs – frequently after each dose, then periodically
- ECG – not performed
- "Medical examination" at screening and each inpatient check-in and check out

Disposition:



Source: CSR Study 083/17, Table 11

Major Safety Findings:
The CSR states that there were no major safety findings (deaths, non-fatal serious adverse events, or adverse events leading to discontinuation).

Common Adverse Events:
Regarding common adverse events, the CSR states:

12.2.3 Analysis of Adverse Events

All the subjects were monitored for the safety and wellbeing during entire duration of the study.

No adverse events were observed during in-house of the study.

No adverse events were reported in during post study evaluation.

Comments: There were no significant findings for the vital signs. Overall, the safety findings are typical for a Phase 1 study in healthy volunteers and did not reveal formulation-specific concerns.

Study 915/22
Objective: Compare fasted PK of Vyscoxa vs. Celebrex at 200 mg and food effect for Vyscoxa at 200 mg
Design:

- Open-label, cross-over, 3-period, single-dose
- Inpatient from Day -1 to 36 hours post dose each period
- At least 7 days washout between periods

Population: Healthy volunteers in the Czech Republic
N: 54 (25F/29M)
Monitoring:

- Adverse events – during inpatient periods and at follow-up
- Vital signs (screening, end of inpatient, end-of-study)
- PE – screening and EOS
- Hematology, chemistry, U/A – screening and EOS
- ECG – screening only

Disposition:

Item	Number of Subjects
Recruited	135
Informed consent signed	86
Eligible for the Study	65 (54 + 11 STBY)
Started Study Period 1	54
Drop-out during Study Period 1	0
Drop-out between Study Period 1 and 2	0
Interrupted before Study Period 2	1[1)]
Started Study Period 2	53
Drop-out during Study Period 2	0
Drop-out between Study Period 2 and 3	3[2)]
Started Study Period 3	51
Drop-out during Study Period 3	0
Completed all 3 periods	**51**

1) Subject No. (b) (6) recruitment No. (b) (6) interrupted on D -1 of Study Period 2 due to AE on August 21, 2023.
2) Subject No. (b) (6) recruitment No. (b) (6) dropped-out on D -1 of Study Period 3, on August 28, 2023, due to personal reasons. Subject No. (b) (6) recruitment No. (b) (6) dropped-out on D -1 of Study Period 3, on August 28, 2023, due to personal reasons. Subject No. (b) (6) recruitment No. (b) (6) dropped-out on D -1 of Study Period 3, on August 28, 2023, due to personal reasons.

Source: Table 9, CSR

Major Safety Findings:

- Deaths: none
- Serious Adverse Events: none
- Discontinuations
  - Nausea, diarrhea, burning eyes after one dose of suspension (200 mg, fasted)
  - "Personal reasons" after two doses of suspension (fasted and fed, 200 mg)
  - "Personal reasons" after two doses of 200 mg suspension/fasted and 200 mg of reference/fasted

Common Adverse Events:
There were a total of eight non-serious AEs, two after suspension/fed, two after reference/fasted, and four after suspension/fasted. The AEs were nonspecific: Headache, dysmenorrhea, and nausea. These are not unusual in a study in healthy volunteers.

Comments: There were no significant findings for the labs or vital signs. Overall, the safety findings are typical for a phase 1 study in healthy volunteers and did not reveal formulation-specific concerns.

9. Advisory Committee Meeting

This product was not discussed at Advisory Committee.

10. Pediatrics

Vyscoxa is the subject of an Agreed iPSP. Pediatric studies on OA, RA, JRA, and AS were waived. This NDA was discussed at a meeting of the Pediatric Review Committee (PeRC) on June 3, 2025. PeRC agreed with full waiver for OA, RA, AS, and JIA/JRA.

There was a discussion about the food effect observed and whether this would affect approval of the JIA/JRA indication. In the end, in light of the MPPRC's discussion (described below), the PeRC did not object to approving the product in pediatric patients. However, this should not be considered a full endorsement because there was some concern about the increased exposure to celecoxib.

Regarding the effectiveness of risk mitigation via labeling, PeRC presented both sides. On one hand, the parent might be more attentive to the direction to take on an empty stomach although there is also an imperative to get a picky eater to eat.

In the end, PeRC recommended adding labeling that the potential for GI intolerance be noted in labeling and parents encouraged to discontinue Tx with Vyscoxa if that occurred. However, one member of PeRC noted that the risks of GI toxicity in children seem to be limited to tolerability.

11. Other Relevant Regulatory Issues

This application was discussed at a Medical Policy and Program Review Council (MPPRC) meeting on May 7, 2025. In response to the question of whether the increased systemic exposure in the fed state justifies a Complete Response (CR) Action, seven out of nine Council members recommended that this application should not be CR'ed. Notably, the Council did not recommend Approval but opined that the application should not be CR'ed on the basis of risk of increased exposure in the fed state.

The Council opined that a CR would be inappropriate for the reasons listed below. Reviewer comments follow each reason:

1. Celebrex is approved to a maximum dosage of 400 mg once-a-day for ankylosing spondylitis. Vyscoxa would have comparable exposures at 200 mg twice-a-day, even in the fed state. Therefore, the worst-case Vyscoxa exposures are not higher than what is approved for Celebrex, and the safety of doses higher than 200 mg is covered by the approved Celebrex labeling.

Reviewer Comment:

First of all, the Applicant did not make this argument. MPPRC is making this argument to justify that the review team's safety concerns with Vyscoxa in the fed state can be adequately addressed by the Agency's previous findings of safety for Celebrex at higher doses. If approved, the Agency's rationale would have to be publicly articulated in the review. Using an Agency-conjured rationale for approval to address serious safety concerns could set a poorly considered precedent.

Regardless, I do not agree with MPPRC's argument. I reviewed the Agency reviews for Celebrex and pertinent correspondence and other records related to the safety review of NSAIDs and coxibs.

The AS indication was approved on July 29, 2005 (Supplement 18). The clinical review indicates that the 400 mg dose was approved based on a phase 3 study (Study N49-01-02-193) that compared Celebrex 200 mg, Celebrex 400 mg, naproxen 500 mg, and placebo. The review states, "Although there was little difference in the mean change from baseline of the three co-primaries between the 200 mg and 400 mg dose, support for the 400 mg dose comes from the responder analysis. There were more responders for the celecoxib 400 mg dose at 53% versus the celecoxib 200 mg dose at 44% at both weeks 6 and 12.

I compared the labels approved on February 9, 2005 and July 29, 2005. The latter PI contains, "Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals," while the antecedent PI does not. Therefore, the review team both acknowledged that there may be benefit to the 400 mg dose and it introduced the "lowest dose/shortest duration" paradigm at the same time. The decision was defensible at that time because the Agency also added that use of the 400 mg dose should be a conscious decision on the part of the prescriber. The dosing and administration for AS reads, "If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options." In this case, the dose is intentionally increased with the goal of increasing potential analgesic benefit to the patient.

The key difference here is that patients who take Vyscoxa with food could be <u>unintentionally</u> exposing themselves to higher risks. Unlike with Celebrex, where increased risk is recognized after a deliberate decision to increase dose after at least 6 weeks of tolerability in a specific subset of patients prescribed the drug (patients with AS), the increased risks of Vyscoxa taken accidentally with food may occur at any time the drug is administered and without clear added benefit to the patient, who may be prescribed for any of the approved indications. I note that a February 10-11, 2014, Advisory Committee meeting was held to discuss

NSAID safety data published after 2005. In the discussion for Question 3, the minutes read, "Despite the close vote, the comments made during discussion were all very similar and conveyed the message that no one should interpret the label to mean that there is a risk-free period, and reiterated that patients should take the lowest dose for the shortest period of time possible." Subsequent to the Advisory Committee meeting, an NSAID class Safety Labeling Change (SLC) to the Boxed Warnings, Warnings, Patient Counseling Information, and Medication Guide were all required (July 9, 2015 SLC Notification Letter).

I further note that, since the 2005 AS approval, the paradigm for the use of NSAIDs has strengthened and become doctrinal. In 2023, Minhas et al[1] published recommendations for NSAIDs in Rheumatologic Disease Clinics of North America. Their final recommendations are imaged below. The lowest dose/shortest duration recommendation appears first.

Box 1
Clinical guide to NSAID use in patients with consideration of cardiovascular risk using a whole patient approach

Use the lowest effective NSAID dose for the shortest period of time.

Depending on the site and intensity of the pain, a topical NSAID might be helpful.

Given that the onset of risk of acute MI occurred in the first week and appeared greatest in the first month of treatment with higher doses, prescribers should engage in shared decision-making with patients and consider weighing the risks and benefits of NSAIDs before instituting treatment, particularly for higher doses.

If concomitant use of corticosteroids is needed, use the lowest glucocorticoid dose (ideally <7.5 mg of prednisone or equivalent for the shortest possible time while continuing to control disease activity).[30]

This discussion should also include weighing the risks of NSAIDs versus the benefits of improved pain control providing increased functional mobility, which will in turn provide other health benefits. Untreated pain can lead patients to avoid physical activity and affects the quality of life in the context of physical function, pain, energy, emotional, social, and mental functions.[40]

Create a pain management toolkit for patients, with NSAIDs being 1 tool in their toolbelt. Incorporate nonpharmacologic therapies, transcutaneous electrical nerve stimulation (TENS) units, physical therapy, occupational therapy, myofascial release, and mindfulness, all providing additive effects for pain control.

As routine assessment of pain score is a difficult metric for assessment and monitoring, monitoring pain-related interference and creation of functional goals can be effective therapeutic targets.

Keep a patient pain/effect diary or apps and regularly review this at patient visits.

Regularly monitor for drug adverse events, including initial BP check 1 week after initiation of NSAIDs, with BP checks at every visit and blood counts and renal function assessed at least yearly.[41]

In patients with some type of CV risk,
- Consider starting with naproxen + PPI or ibuprofen + PPI
- Celecoxib 200 mg daily may be a good alternative; higher doses and twice daily regimens are not recommended
- In patients taking aspirin, recommend naproxen + PPI 2 hours after taking aspirin, or celecoxib 200 mg + PPI.
- Avoid the use of diclofenac

[1] Minhas D, Nidhaan A, Husni ME. Recommendations for the Use of Nonsteroidal Anti-inflammatory Drugs and Cardiovascular Disease Risk: Decades Later, Any New Lessons Learned? Rheum Dis Clin North Am. 2023 Feb;49(1):179-191. doi: 10.1016/j.rdc.2022.08.006. PMID: 36424024.

It is difficult to believe that a 400 mg dose of Celebrex would be approved today, particularly given the modest benefit observed compared to 200 mg. Because we are reviewing Vyscoxa in 2025, I do not think it is defensible to cite this 20-year-old labeling to support approval of Vyscoxa.

Moreover, among the indications sought by this Applicant for Vyscoxa, the reference to a 400 mg dose in the RLD relates only to the AS indication. The Celebrex label makes no determination of safety or efficacy for doses greater than 200 mg celecoxib for any of the other proposed indications. The efficacy and safety of higher-than-intended exposures for OA, RA, and JRA are not covered by the Celebrex labeling; thus, the benefit-risk of higher exposure for those indications seems even less favorable than for AS.

2. There may be unique benefit in a niche population (dysphagia, lacking manual dexterity to open a capsule).

   Reviewer Comment:
   It is possible that there is a small subset of patients with dysphagia and who cannot manipulate a capsule to release the contents. However, that is a subset of a subset, and it is possible that such a patient with those limitations would have a caretaker or someone who can assist with medications. Also, while off-label, Elyxyb (celecoxib oral solution) could be used in this small number of patients. It seems unlikely to me that the number of patients fitting this description will outnumber the patients who will be noncompliant with labeling to take on an empty stomach. Last, patients fitting this clinical picture of dysphagia and lack of manual dexterity are likely to be elderly and have co-morbid medical conditions (e.g., neurological disorders, gastroesophageal reflux disease), factors that make them more susceptible to NSAID-related risks (Wongrapkanich[2]).

3. Labeling to take on an empty stomach will effectively mitigate the formulation liability.

   Reviewer Comment:

   The indications sought by this Applicant are all musculoskeletal. While medication compliance is less than perfect in all therapeutic areas, medication adherence data are available for rheumatologic conditions. In fact, Kelly et al [3]

[2] Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging Dis. 2018 Feb 1;9(1):143-150. doi: 10.14336/AD.2017.0306. PMID: 29392089; PMCID: PMC5772852.

[3] Kelly A, Tong A, Tymms K, March L, Craig JC, De Vera M, Evans V, Hassett G, Toupin-April K, van den Bemt B, Teixeira-Pinto A, Alten R, Bartlett SJ, Campbell W, Dawson T, Gill M, Hebing R, Meara A, Nieuwlaat R, Shaw Y, Singh JA, Suarez-Almazor M, Sumpton D, Wong P, Christensen R, Beaton D, de Wit M, Tugwell P; OMERACT-Adherence Group. Outcome Measures in Rheumatology - Interventions for medication Adherence (OMERACT-

published a protocol with the goal of demonstrating improvement in patient compliance in rheumatology. The authors note, "However, rates of medication adherence have been reported to be as low as 10% in gout, 30% in RA and 45% in osteoporosis."

Should we pursue labeling as the risk mitigation here, this would require prescribers and patients to be knowledgeable that (unique among all other NSAIDs) this particular NSAID requires dosing on an empty stomach for every single dose. NSAID dosing on an empty stomach contradicts nearly universal medical advice and patient preference which is to take an NSAID with food. Rainsford and Bjarnason[4] found little scientific evidence to support this practice. Nevertheless, Rainsford states:

> *However, to ingest medicines with, before or after intake of food is an equally common with most drugs, as evident in drug or patient information leaflets. However, in the case of NSAIDs these recommendations are widely evident in the published literature. Accordingly, taking NSAIDs with fluids or in conjunction with foods is the advice in most European countries… The US Food and Drug Administration patient information leaflet 'Drug Facts' recommends taking NSAIDs 'with food or milk if stomach upset occurs… Hence most regulatory bodies, and the vast majority of OTC package information leaflets, advise taking NSAIDs with food and/or fluids…*

The available evidence does not support that labeling alone is sufficient to mitigate the risk of taking Vyscoxa with food. Therefore, actions beyond labeling must be considered to mitigate risk.

4. Other risk mitigation strategies, including a medication guide and/or postmarketing requirements, can effectively decrease the risk of unintentional increased exposure.

Reviewer Comment:

Various members of MPPRC suggested additional strategies to mitigate the risk of taking Vyscoxa with food, including a medication guide, warning labels to take the drug on an empty stomach, and/or postmarketing requirements. However, there is insufficient data to support that any of these strategies would effectively promote the safe use of a single formulation of a single drug whose other formulations and other drug class members are administered according to a different (and seemingly opposite) paradigm.

Adherence) Core Domain Set for Trials of Interventions for Medication Adherence in Rheumatology: 5 Phase Study Protocol. Trials. 2018 Mar 27;19(1):204. doi: 10.1186/s13063-018-2565-z. PMID: 29587864; PMCID: PMC5870260.

[4] Rainsford KD, Bjarnason I. NSAIDs: take with food or after fasting? J Pharm Pharmacol. 2012 Apr;64(4):465-9. doi: 10.1111/j.2042-7158.2011.01406.x. Epub 2011 Nov 18. PMID: 22420652.

Although a medication guide would contain the relevant information (that the medication should be taken on an empty stomach and that there is a risk of unintentional overdose when taken with food), it is not clear whether it would be an effective risk mitigation strategy for this product. Although medication guides are a common strategy to disseminate safety information to patients, their utility in mitigating the risk of adverse events is questionable.[5] It should also be noted that all NSAIDs already have a Medication Guide, and it is conceivable that a patient who has already received one for another prescription NSAID (highly likely in the target patient population) would not recognize the key difference between a medication guide for Vyscoxa and all other NSAID medication guides. Lastly, practically speaking, not all healthcare providers or pharmacists will be able to ensure consistency in providing and reviewing the information in the medication guide with patients.

Similarly, warning labels or stickers on prescriptions are of questionable benefit. While container-affixed labels may be seen by patients, there are concerns that such labels may not attract the attention of patients (particularly older patients), may not be recalled, or may not be clearly understood.[6] Thus, container-affixed warning labels do not seem adequate to mitigate the risk of noncompliance with the drug labeling.

Postmarketing requirements (PMRs) considered include a study to determine the impact of a low-fat diet on Vyscoxa exposure, which would reflect a common, clinically relevant scenario. The information from such a study could provide information relevant to improve the label for this product. However, a PMR for information that may more fully characterize a safety concern does not adequately ameliorate a known concern that arguably precludes approval of the product.

Another PMR proposed by an MPPRC member was a study to evaluate the long-term risks of cardiovascular and GI risks of taking the drug in the fasting versus the fed state. While it was acknowledged that such a study could provide useful information, it would be highly infeasible given the very small population of patients likely to use this drug and that, even though these adverse events are serious and well-known, they are relatively rare.

All of this being said, the Medication Guide was edited to prominently add "Do not take VYSCOXA with food. VYSCOXA must be taken on an empty stomach at least 2 hours before or 1 hour after food. If you cannot tolerate VYSCOXA on an empty stomach, stop taking VYSCOXA and tell your healthcare provider.

---

[5] Wolf MS, King J, Wilson EA, Curtis LM, Bailey SC, Duhig J, Russell A, Bergeron A, Daly A, Parker RM, Davis TC, Shrank WH, Lambert B. Usability of FDA-approved medication guides. J Gen Intern Med. 2012 Dec;27(12):1714-20.

[6] Bailey SC, Navaratnam P, Black H, Russell AL, Wolf MS. Advancing best practices for prescription drug labeling. Annals of Pharmacotherapy. 2015 Nov;49(11):1222-36.

12. Labeling

The fact that 400 mg of Vyscoxa (fasted) results in higher exposures than 400 mg of Celebrex (fasted) and questions around pediatric use resulted in codaDOSE abandoning the acute pain and dysmenorrhea indications for Celebrex. The labeling submitted in the original NDA also included appropriate edits to reflect the new formulation (oral suspension vs. capsule) and the Pregnancy and Lactation information were updated and made consistent with PLLR.

Given that the Agency's only risk mitigation for the food effect is labeling, I endeavored to maximize the language around the food effect in clinical sections of the labeling. Detailed comments for changes made to nonclinical sections of labeling are described in the individual discipline reviews. A summary of paraphrased and summarized key changes follows.

Original	July 2025 FDA Markup	Rationale
Section 1: Limitation of Use was limited to not use Vyscoxa for the acute Celebrex indications.	Added "VYSCOXA must be administered on an empty stomach at least 2 hours before or 1 hour after food. Taking VYSCOXA with food results in plasma exposures of celecoxib up to 50% higher than intended. If patients cannot tolerate VYSCOXA in the fasted state, discontinue use of VYSCOXA (reference Sections 12, 2.1, 5).	Risk mitigation for PK mismatch in the fed state
Section 2: No description of recommendation to take on an empty stomach.	Added, "VYSCOXA must be taken on an empty stomach at least 2 hours before or 1 hour after food [see Clinical Pharmacology (12.3)]	Risk mitigation for PK mismatch in the fed state
Sections 6 and 14: Implied that codaDOSE had generated substantial data that was conducted to support the Celebrex NDA and supplements	Generally addressed by substituting "VYSCOXA" with "another formulation of celecoxib".	Clarity
Section 12:	In conjunction with the Clinical Pharmacology team, the original language was edited.	Clarity.
Medication Guide	As noted elsewhere, advice regarding to take on an empty stomach is prominently displayed.	Risk mitigation for PK mismatch in the fed state

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

I recommend that the following comments be conveyed in a Complete Response Letter:

> The benefit-to-risk relationship for celecoxib oral suspension (COS) is unfavorable. Benefit is generalized from your scientific linkage to the Listed Drug (Celebrex®), and you have conducted no clinical studies to further evaluate effectiveness. Therefore, the benefits of COS cannot exceed those of Celebrex.
>
> However, COS has a known formulation liability in that administration with food results in significantly higher celecoxib exposures compared to the Listed Drug, even at the 200 mg dose. NSAID-related risks (major cardiovascular adverse events, enteropathy, and renovascular adverse events) are dose and duration dependent. Thus, patients who take COS with food will have higher-than-intended celecoxib levels and be at higher risk for NSAID-related adverse reactions than patients on other formulations of celecoxib or on other NSAIDs.
>
> To address this deficiency, reformulate the product to minimize or eliminate the food effect. Alternatively, demonstrate that prescribers and patients can identify your product and have high compliance with instructions to dose consistently on an empty stomach. In addition, should you choose to mitigate this risk through labeling and patient education, submit data to support the tolerability of this product, at the maximum dose, in the fasted state given that NSAIDs used for chronic conditions are usually taken with food. These data should be generated in subjects with the condition to be treated. The single-dose comparative bioavailability data in healthy volunteers do not suffice to address this question.

However, I understand that Vyscoxa will be approved over my recommendation. I have worked diligently on labeling to that goal. I do not recommend any extra language beyond that in the Approval Letter template for this application.

APPENDIX: Potentially pertinent precedents: Analgesics with substantial food effect

Xtampza ER (NDA 208090) is an extended-release formulation of oxycodone. The product has purported "abuse-deterrent" properties (ADF). Phase 1 studies showed that Xtampza has substantial food effect related to the fat and calorie content of the meal consumed. Table #, below shows summary data for the food effect.

Table #: Summary of food effect data

Parameter	Fasted (Reference) LSGM	LFLC LSGM	Ratio %[a] (90% CI)	MFMC LSGM	Ratio %[a] (90% CI)	HFHC LSGM	Ratio %[a] (90% CI)
Cmax (ng/mL)	29.84	35.9	**120** (112 – 128)	54.9	**184.2** (172 – 196)	49.75	**166.7** (156 – 177)
AUClast (ng.h/mL)	317.9	372.6	117 (111 – 123)	440.7	**138** (132 - 145)	472.6	**148.6** (141 – 156)
AUCinf (ng.h/mL)	337.8	384.02	113.7 (108 - 119)	451.2	**133.6** (127 – 139)	485.5	**143.7** (137 – 150)

LFLC: Low-fat Low-calorie; MFMC: Medium-fat Medium calorie; HFHC: High-fat High-calorie.
[a]Ratio to fasted Xtampza treatment and 90% CI. Bold face numbers indicate significant increase in PK parameter as indicated by the 90% CI beyond the 80 – 125 limits.

Source: Table 2 from Summary Review for Regulatory Action, NDA 208090

On September 11, 2015, the product was discussed at Advisory Committee (AC) prior to Approval, mostly due to a requirement to take all ADF opioids to AC at that time. The approval documents indicate that while the review team was concerned about the food effect, the purported ADF features and the fact that the formulation (a capsule) could be opened and the contents sprinkled on soft food was a compelling factor to support approval.

The Decisional Summary reads in part:

> The Applicant has provided adequate evidence of efficacy and safety to support approval for the proposed indication, even with the demonstrated effect of food on the bioavailability of oxycodone from Xtampza. In addition, the Applicant has provided adequate evidence to support that Xtampza has properties likely to deter abuse by the intranasal and intravenous routes of administration. However, what stands out about this product is that the formulation is resistant to dose dumping when chewed, crushed, and can be sprinkled on soft food for dosing in patients with dysphagia This results in a safety advantage for Xtampza over other, currently approved extended-release oxycodone products that benefits the intended patient population. These properties are the result of the novel formulation.

The Clinical Pharmacology review reads in part:

> The food-effect of Xtampza was discussed at the Advisory committee meeting on September 11, 2015. The committee discussed the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, as well as

potential fluctuations in plasma oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committee was asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse, and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The committee was asked to vote on whether this product should be approved for marketing in the United States. The Advisory Committee recommended unanimous approval probably based on the following reasons:

Pertinent labeling reads:

> XTAMPZA ER is administered, twice daily, every 12 hours, and must be taken with food. Instruct patients to take XTAMPZA ER capsules with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved

The following examples of NSAIDs with notable food effect were identified from Naraharisetti et al.[7]

Celebrex® (NDA 020998)

Section 12.3 of the package insert notes that exposure is less than proportional at higher doses (over 200 mg). The labeling also notes that, when taken with a high-fat meal, Tmax is delayed, and the AUC increases 10% to 20%. Thus, for doses of 200 mg or less, Celebrex® can be taken without regard to food. However, to improve absorption at the dose of 400 mg, Section 1.3 recommends to administer the 400 mg dose with food. The 400 mg dose has limited utility. It is used as a loading dose for the acute indications (acute pain and primary dysmenorrhea). It is also an option for ankylosing spondylitis for patients who do not respond to a 200 mg total daily dose.

Zorvolex (NDA 204592)

Zorvolex is a reformation of diclofenac as a capsule approved for acute pain (AP) and osteoarthritis (OA). The Phase 1 studies showed that the T_{max} was slightly delayed in the fed state (3.32 hours vs. 2.33 hours for immediate-release diclofenac tablets). One comparison showed a difference of 2.32 hours (3.32 vs. 1.00). Section 12.3 of the package insert indicates that there was an effect on C_{max} (48% lower in the fed state).

The difference in C_{max} and T_{max} is not clinically meaningful for a drug used chronically, as one would for OA. However, there was concern about the implications of a delay in onset of action for AP. Patients may redose too quickly leading to a greater than intended exposure to diclofenac. This finding was addressed in the labeling by noting that "Taking ZORVOLEX with food may cause a reduction in effectiveness compared to taking ZORVOLEX on an empty stomach." in Section 2.1. The package insert notes the effects on C_{max} of food in Section 12.3.

[7] Naraharisetti SB, Srour S, Xu Y, Lee DJ, Hertz SH, Sahajwalla C. Effects of Food on Bioavailability of Analgesics; Resulting Dosage and Administration Recommendations. Pain Med. 2020 Nov 1;21(11):2877-2892. doi: 10.1093/pm/pnaa046. PMID: 32274507.

Qmiiz (NDA 211210)

Qmiiz is a reformulation of meloxicam as an orally disintegrating tablet. The product is approved for OA, rheumatoid arthritis, and juvenile rheumatoid arthritis. The Phase 1 studies showed no food effect on C_{max} or AUC although there was a delay in T_{max}. Because the product is approved for chronic use indications, this finding was not considered clinically meaningful.

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