Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
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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

Original	July 2025 FDA Markup	Rationale
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

Routine postmarketing surveillance is appropriate for this product. I do not recommend any postmarketing Risk Evaluation and Mitigation Strategies nor any other Postmarking Requirements or Postmarketing Commitments.

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

/s/

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