CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212157Orig1s000

SUMMARY REVIEW

Summary Review

Date	May 5, 2020
From	Heather Fitter, MD Nick Kozauer, MD
Subject	Summary Review
NDA #	212157
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	July 5, 2019
PDUFA Goal Date	May 5, 2020
Proprietary Name	Elyxyb
Established or Proper Names	DFN-15, Celecoxib
Dosage Form	Oral solution (25 mg/mL)
Recommended Dosing Regimen	120 mg at the onset of migraine: maximum dose within 24 hours is 120 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Elyxyb (celecoxib oral solution) is a nonsteroidal anti-inflammatory drug (NSAID) that is a cyclo-oxygenase 2 (COX-2) inhibitor. The applicant is seeking an indication for the acute treatment of migraine with and without aura in adults. Celecoxib is marketed as Celebrex, and has multiple indications but is not indicated for the acute treatment of migraine. Therefore, the applicant has conducted two adequate and well-controlled efficacy studies with Elyxyb to support efficacy for the migraine indication, and largely relies on the Celecoxib label to support the safety of its product, using a 505(b)(2) approach.

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans (5-$HT_{1B/1D}$ receptor agonists), lasmiditan (5-HT_{1F} receptor agonist), ubrogepant and rimegepant (CGRP antagonists), dihydroergotamine (DHE), and NSAIDs; the latter of which can be used alone (Cambia) or in combination with a triptan (Treximet). In addition, there are over-the-counter products approved for the acute treatment of migraine.

The efficacy of Elyxyb was demonstrated in two identical adequate and well-controlled studies. The studies used well-validated and clinically meaningful co-primary endpoints to establish efficacy; the proportion of patients who were pain-free and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. Both studies evaluated the efficacy of a single dose, 120 mg, as compared to placebo. One study demonstrated statistically significant treatment effects on both co-primary endpoints. The other study demonstrated a highly statistically significant treatment effect on MBS freedom at 2 hours post-dose, and a strong numerical trend favoring Elyxyb on pain freedom at 2 hours post-dose. The treatment effect size for pain freedom at 2 hours post-dose was approximately 7-14% greater than placebo in the two studies (Elyxyb responder rate of approximately 33-36%). The treatment effect size for MBS-freedom at 2 hours post-dose was approximately 13-14% greater than placebo in the two studies (Elyxyb responder rate of approximately 58-59%). The efficacy of a second dose was not studied in this development program. These data support the efficacy of Elyxyb for the proposed indication based on the established effect on MBS freedom in both trials and strength of the effect on pain freedom in one trial in the context of a strong trend towards efficacy on this endpoint in the other, in the setting of a drug from a class that has known analgesic properties.

The safety profile of Elyxyb after a single dose was evaluated in the two controlled efficacy studies, while long-term safety was derived from the safety experience with Celebrex. The Celebrex prescribing information (PI) includes boxed warnings for risks of serious cardiovascular and

gastrointestinal events, as well as Warnings and Precautions sections pertaining to hepatoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, premature closure of fetal ductus arteriosus, and hematologic toxicity. These risks will be included in the Elyxyb label. A Warning and Precaution section for medication overuse headache will also be included in the Elyxyb PI as this risk is associated with overuse of NSAIDs for the acute treatment of migraine. In addition, the efficacy trials conducted with Elyxyb demonstrated an increased incidence of dysgeusia in Elyxyb treated patients over placebo (3.0% versus 1.2%, respectively).

The risk/benefit profile of Elyxyb is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. There is no evidence to suggest that Elyxyb is more effective than other FDA-approved drugs for the acute treatment of migraine; however, Elyxyb offers availability of another treatment option. Labeling will clearly convey the safety profile demonstrated with extensive experience of Celebrex and will also describe the increase in the incidence of dysgeusia with the use of Elyxyb as compared with placebo.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Current Treatment Options</td><td>• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamine (DHE), lasmiditan, CGRP antagonists and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter which can be used alone or in combination with a triptan. In addition, there are several over-the-counter drugs marketed for migraine.</td><td>Several classes of drugs are indicated for the acute treatment of migraine with and without aura in adults. However, many patients still do not respond adequately to these therapies.

Elyxyb offers another treatment option for migraine patients.</td></tr>
<tr><td>Benefit</td><td>• The efficacy of Elyxyb was demonstrated in two adequate and well-controlled clinical studies (Studies 006 and 007). The studies used well-validated and clinically meaningful endpoints to evaluate efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. Results are summarized in the table below; comparisons between the Elyxyb group and placebo are highly statistically significant for MBS freedom at 2 hours, and statistically significant for pain freedom at 2 hours in Study 007, while demonstrating a strong numerical trend in Study 006.

<table>
<tr><th></th><th>PF at 2 hours (%)</th><th>Placebo corrected PF (%)</th><th>MBS free at 2 hours (%)</th><th>Placebo corrected MBS free (%)</th></tr>
<tr><td>Study 006</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>25.3</td><td></td><td>44.4</td><td></td></tr>
<tr><td>Elyxyb 120 mg</td><td>32.4[a]</td><td>7</td><td>58</td><td>14</td></tr>
<tr><td>Study 007</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>21</td><td></td><td>43.9</td><td></td></tr>
<tr><td>Elyxyb 120 mg</td><td>35.1</td><td>14</td><td>56.8</td><td>13</td></tr>
</table>
a not statistically significant

• A second dose to treat a single migraine attack was not evaluated in the clinical efficacy studies.
• Other NSAIDS have demonstrated efficacy for the acute</td><td>Elyxyb is effective for the acute treatment of a migraine with and without aura in adults.

These data support the efficacy of Elyxyb for the proposed indication based on the established effect on MBS freedom in both trials and strength of the effect on pain freedom in one trial in the context of a strong trend towards efficacy on this endpoint in the other, in the setting of a drug from a class that has known analgesic properties.

The recommended doses of Elyxyb for marketing will be 120 mg. The maximum dose recommended in a 24-hour period is 120 mg. The efficacy and safety of a second dose for a single migraine attack was not evaluated.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment of migraine, such as Cambia and Vioxx; Cambia is currently available, while Vioxx is no longer marketed. • Celecoxib is an NSAID with an acute pain indication.	
Risk and Risk Management	• Supportive safety data for Elyxyb is provided by the listed drug, Celebrex, which has been marketed since 1998. • The Celebrex label includes a boxed warning for serious cardiovascular and gastrointestinal events, as well as Warnings and Precautions sections pertaining to hepatoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, premature closure of fetal ductus arteriosus, and hematologic toxicity. • A Warning and Precaution section will be added to the Elyxyb label for medication overuse headache as this is a risk associated with NSAIDs used for the treatment of acute migraine. • There were no serious safety issues identified in the controlled clinical trials conducted with Elyxyb. • The incidence of dysgeusia in the controlled clinical trials was increased in patients that received Elyxyb compared to placebo (3.0% versus 1.2%, respectively). Other uncertainties • Safety and efficacy in pediatric migraine patients has not been established.	There were no significant safety findings that would preclude approval of Elyxyb. Adequate labeling will address the identified safety issues. Information from the Celebrex label will be used to support long term safety of Elyxyb. A Warning and Precaution section for medication overuse headache will be added to the label, as well as information about the increased incidence of dysgeusia seen in the controlled clinical trials with Elyxyb, in the Elyxyb treated group as compared to the placebo group. Since safety and efficacy of Elyxyb in pediatric migraine patients has not been established, a study to evaluate Elyxyb in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA).

2. Background

This review discusses the data presented by Dr. Reddy's Laboratory (the applicant) in support of a 505(b)(2) new drug application (NDA) for DFN-15 (Elyxyb), a celecoxib oral solution, for the acute treatment of migraine with and without aura in adults. The applicant is relying on the listed drug (LD), Celebrex capsules (NDA 020998), to support the safety of its product.

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is selective for cyclooxygenase-2 (COX-2). Celecoxib was first approved in 1998 and is currently indicated for the treatment of acute pain, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, and primary dysmenorrhea. Since the marketed formulation of celecoxib is not indicated for the acute treatment of migraine, the applicant has conducted two efficacy studies to support this application.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a range of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders-3 (ICHD-3).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, NSAIDs used alone or in combination with a triptan, a 5-HT_{1F} agonist, (lasmiditan) and CGRP antagonists (ubrogepant and rimegepant). There are also many over-the-counter medications that are labeled for the acute treatment of migraine. Despite the availability of numerous products, not all migraineurs respond well to the available therapies, the use of which can also be limited by safety concerns (e.g., restrictions for the use of triptans, ergotamines, and NSAIDs in patients with cardiovascular (CV) disease and driving restrictions for lasmiditan).

The applicant provides data from two placebo-controlled efficacy trials, Studies DFN-15-006 (referred to as Study 006 in this review) and DFN-15-007 (referred to as Study 007 in this review), in adult patients with migraine with and without aura to support the efficacy of DFN-15 for the proposed indication.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann (refer to her review for the entire OPQ list of participants in the review of this application).

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The applicant has developed a liquid formulation of celecoxib which contains 25 mg/mL and will be packaged in a single-dose glass bottle containing 4.8 mL of solution (120 mg celecoxib).

Dr. Heimann states that the active pharmaceutical ingredient (API), celecoxib USP, is well characterized and was initially approved in 1998, and is currently marketed under multiple applications. The drug master file (DMF) is adequate to support approval of this NDA.

Dr. Heimann reports that the proposed regulatory specifications for celecoxib oral solution including tests for appearance, identity, assay performance, related substances, preservative content, viscosity, droplet size, and microbiological testing ensure product quality and delivery of the intended dose to the patient. Noncompendial tests are adequately described and validated. The stability data from the registration batches support a 24-month shelf life for the product stored at controlled room temperature.

All facilities that will be involved in commercial manufacture and testing of Elyxyb oral solution are currently acceptable.

The OPQ review concludes that from a quality perspective, the application provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients. The OPQ review team recommends approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

The primary reviewer from the Office of Clinical Pharmacology (OCP) was Dr. Mariam Ahmed and Dr. Sreedharan Sabarinath was the team leader. Dr. Ahmed states that the applicant conducted 8 clinical studies with DFN-15 to support this application. These included four pilot clinical pharmacology (comparative bioavailability) studies in healthy adult subjects with prototype formulations of DFN-15, one proof of concept Phase 2 dose ranging study using a prototype formulation of DFN-15 (50 mg/mL), one pivotal comparative bioavailability study (DFN-15-CD-008: which will be referred to as Study 008 in this review) with the final to-be-marketed formulation of DFN-15 (25 mg/mL) and the listed drug Celebrex capsule 400 mg, and two Phase 3 efficacy studies (006 and 007). Both Phase 3 studies used the final, to-be-marketed formulation of DFN-15.

Dr. Ahmed states that the LD, Celebrex, is available as 50, 100, 200, and 400 mg capsules and is approved for several indications: osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years and older, ankylosing spondylitis, acute pain, and primary dysmenorrhea. In adults, the approved dosage for these indications ranges from 200 mg to 400 mg daily. The recommended dose for acute pain is 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

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twice daily, as needed. As per Celebrex's prescribing information, Celebrex at doses up to 200 mg twice daily can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

The applicant conducted Study 008 to establish a pharmacokinetic (PK) bridge between the to-be-marketed formulation and Celebrex. This was a single-dose, single-center, randomized, three-period crossover study in healthy subjects (N=24) designed to assess the comparative bioavailability of a single dose of 120 mg DFN-15 under fasting conditions relative to a 400 mg Celebrex capsule under fed conditions, and to evaluate the food effect on the rate and extent of absorption of 120 mg DFN-15. The purpose of this trial was to demonstrate that exposures at the applicant's proposed dose of 120 mg DFN-15 in a 24-hour period were less than the exposures at the approved 400 mg dose for Celebrex capsules, thereby allowing the applicant to rely on the safety data from the Celebrex NDA to support its current application.

The plasma celecoxib AUC_{last} and AUC_{inf} following administration of DFN-15 120 mg under fasting conditions were approximately 73% and 72% lower, respectively, compared to the 400 mg Celebrex capsule administered under fed conditions. The peak levels were also lower by approximately 43% for the DFN-15 120 mg compared to the Celebrex capsule. The plasma celecoxib AUC_{last} and AUC_{inf} following administration of DFN-15 120 mg under fed and fasting conditions were similar. However, C_{max} decreased to approximately half that observed under fasting conditions and was delayed by 2 hours after a high-fat meal.

Following administration of 120 mg DFN-15 under fasting condition in 24 healthy subjects, the median plasma T_{max} of celecoxib was 1 hour (range 0.67 to 3.00) compared to 3.5 hours (range 1.65 to 6.00) following 400 mg of celecoxib oral capsule administered under fed conditions. The mean (CV%) peak concentration (C_{max}) and the extent of absorption (AUC) of celecoxib from 120 mg of DFN-15 under fasting conditions was 993 ng/mL (21.9%) and 3568 ng.hr/mL (38.5%), respectively. With high fat food, the T_{max} of celecoxib from DFN-15 was 3 hours (range 0.55 to 4) with about 50% decrease in C_{max} and no change in AUC_{inf} compared to fasting conditions.

Dose proportionality was demonstrated for DFN-15 over a dose range of 120 mg to 240 mg. While the applicant did not study the dose proportionality for this solution for doses below 120 mg, Celebrex has linear PK over the dose range 50 mg to 200 mg. Given the relative bioavailability of DFN-15 relative to Celebrex, a dose of 120 mg DFN-15 is similar to approximately 100 mg of Celebrex in terms of total exposure (AUC_{inf}) and to approximately 200 mg of Celebrex in terms of C_{max}.

The OCP team recommends that DFN-15 120 mg be administered with or without food, and that the maximum dosage in a 24-hour period should be 120 mg, as the efficacy and safety of a second dose were not evaluated in the development program. They recommend a dose adjustment to 60 mg in patients with moderate hepatic impairment and in patients who are known CYP2C9 poor metabolizers. They recommend avoiding use in patients with severe hepatic and renal impairment.

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OCP consulted the Office of Study Integrity and Surveillance (OSIS) to inspect the analytical and the clinical sites for Study 008. The clinical site was inspected, and the final inspection classification is No Action Indicated (NAI). OSIS concluded that no inspection was warranted for the analytical site as the same site was inspected recently with an inspection classification of NAI.

OCP concludes that based on the results of Study 008, the applicant can rely on the Agency's findings of safety for Celebrex capsules.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Viveca Livezey conducted the clinical efficacy review for this application. Dr. Xiang Ling conducted the biometrics review and Dr. Kun Jin was the biometrics team leader.

The applicant conducted two placebo-controlled efficacy trials (Table 1) in adult migraine patients with and without aura: Study 006 and Study 007.

Table 1: Clinical Efficacy Studies

	Population	Treatment Duration	Dose
Study 006	Migraine with and without aura	Double-blind (DB) randomized treatment of a single migraine attack (moderate-severe pain), followed by the option to re-randomize to a second DB period for treatment of another migraine attack (mild-severe pain)	120 mg
Study 007	Migraine with and without aura	DB randomized treatment of a single migraine attack (moderate-severe pain), followed by the option to re-randomize to a second DB period for treatment of another migraine attack (mild-severe pain)	120 mg

Studies 006 and 007

Studies 006 and 007 were identical multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of DFN-15 for the acute treatment of migraine (associated with moderate to severe pain). Patients were randomized in a 1:1 ratio to receive either 120 mg DFN-15 or placebo. Patients had the option of being re-randomized to a second double-blind placebo-controlled period to treat a migraine associated with pain of mild to severe intensity.

Patients eligible for enrollment into the trials were adults 18-75 years of age with a diagnosis of migraine with and without aura, and with 2-8 migraine attacks per month for at least the last 12 months. Patients with medication overuse headache or without stable dosing of a preventive treatment for migraine over the past 30 days were excluded.

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The co-primary endpoints used to evaluate efficacy were the proportion of patients who were headache pain-free at 2 hours, and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours, following the initial dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying migraine attack (defined below). The pain freedom endpoint was assessed using a 0-3 scale, where 0=no pain, 1=mild, 2=moderate, and 3=severe. The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia, and was to be determined prospectively by the patient at the time of a qualifying migraine attack but before administration of study drug. The MBS endpoint was assessed in a binary fashion, as either present or absent. The protocols for both trials also included several secondary endpoints; however, none of the analyses of these endpoints were controlled for Type 1 error and, therefore, they could only be considered to be exploratory.

The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study medication during the first double-blind period to treat a qualifying migraine (associated with moderate-severe intensity pain) and have at least one post-baseline efficacy assessment for either co-primary endpoint. Assessments from the first double-blind period only were used to evaluate efficacy since the second double-blind period was not deemed to be independent of the first double-blind period (these periods are referred to as DB1 and DB2, respectively). Dr. Ling states that she does not consider DB2 as an independent study because the observations from the same patient in both periods are not independent and the outcome in DB1 would provide information on the outcome in DB2. For example, the probability of DB2 headache pain response was much greater for DB1 responders compared to DB1 non-responders. Therefore, the statistical tests and inferences for DB1 and DB2 were based on highly correlated data and were not independent. Only the analyses of DB1 from Study 006 and 007 will be described in this review, as these are the periods used to evaluate efficacy in this application.

The applicant prespecified in the statistical analysis plan that missing primary efficacy endpoint data would be imputed using the last observation carried forward (LOCF) and that results would be displayed as both LOCF data and observed data [observed cases (OC)], separately. In addition, the planned analysis called for excluding patients who took rescue medication prior to 2 hours post-dose. The use of the LOCF to handle missing data for the primary analysis was determined to be acceptable; however, patients that took rescue medication prior to 2 hours post-dose were considered as non-responders in the Division's primary efficacy analyses reported in this review, the standard approach in trials of drugs for the acute treatment of migraine. The efficacy of a second dose of study medication to treat either an unresolved headache or a headache that returned after initial resolution was not tested.

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Results

Studies 006 and 007

The median age of the patients in both trials was 39-41 years. Eighty-two to 88% of patients were female, and 70-78% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups in both trials. The average age of onset of migraine was 22 years, the median duration of migraine history was 16-17 years, and approximately 56% of patients experienced migraine both with and without aura.

Co-primary endpoints

Table 2 presents the results of the primary efficacy analyses for Studies 006 and 007.

Table 2: Studies 006 and 007- Co-primary Endpoint Analyses (source: modified from Dr. Livezey's review Table 25)

Endpoint	Study 006		Study 007	
	Placebo	DFN-15 120 mg	Placebo	DFN-15 120 mg
Pain Freedom at 2 Hours (N) % Responders Difference from placebo (%) p-value	273 25.3	284 32.4 7 0.076	271 21.0	279 35.1 14 <0.001
MBS Freedom at 2 Hours (N) % Responders Difference from placebo(%) p-value	234 44.4	245 58.0 14 0.003	237 43.9	236 56.8 13 0.006

Study 007 demonstrated a robust effect on both co-primary endpoints, while Study 006 demonstrated a robust effect on MBS freedom at 2 hours with a strong numerical trend demonstrated on pain freedom at 2 hours.

Sensitivity analyses for the co-primary endpoints

Dr. Ling reports that to evaluate the strength of the primary efficacy analyses, she conducted additional sensitivity analyses using different methods to impute missing data. One method was to use the Next Observations Carried Backward (NOCB) for patients who did not have data by 2 hours post-dose but had data from greater than 2 hours to 24 hours post-dose. The

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other method was a worst-case type of imputation in which only the additional NOCB responders in the placebo group were counted, while all patients in the DFN-15 group with missing 2-hour data were considered as non-responders. The results of both of these sensitivity analyses were consistent with the primary efficacy analyses and are displayed in Table 3 and Table 4 below.

Table 3: Study 006-Analysis of Pain Freedom at 2 hours with Missing Data Imputation (source: Dr. Ling's review Table 15)

	Placebo	**DFN-15**
NOCB		
Number of assessments	280	286
Number of responses	71	94
Proportion (%) (95% CI)	25.4 (20.4, 30.9)	32.8 (27.5, 38.6)
P-value		0.052
Odds ratio (95% CI)		1.44 (1.00, 2.08)
Worst-Case Imputation		
Number of assessments	280	286
Number of responses	71	92
Proportion (%) (95% CI)	25.4 (20.4, 30.9)	32.2 (26.8, 37.9)
P-value		0.078
Odds ratio (95% CI)		1.40 (0.97, 2.01)

Table 4: Study 007-Analyses of Pain Freedom at 2 hours with Missing Data Imputation (source: Dr. Ling's review Table 6)

	Placebo	**DFN-15**
NOCB		
Number of assessments	276	282
Number of responses	59	99
Proportion (%) (95% CI)	21.4 (16.7, 26.7)	35.1 (29.5, 41.0)
P-value		<0.001
Odds ratio (95% CI)		1.99 (1.36, 2.90)
Worst-Case Imputation		
Number of assessments	276	282
Number of responses	59	98
Proportion (%) (95% CI)	21.4 (16.7, 26.7)	34.8 (29.2, 40.6)
P-value		<0.001
Odds ratio (95% CI)		1.96 (1.34, 2.86)

The analyses of all of the secondary endpoints in both studies, although generally consistent with the results of the primary efficacy analyses, were only considered exploratory as they

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were not controlled for Type I error; therefore, the results of these analyses are not capable of supporting the efficacy of DFN-15 and will not be described in this review.

Drs. Livezey and Ling conclude that the efficacy data from Studies 006 and 007 support the approval of DFN-15 for the proposed indication. Dr. Livezey's review cites the strength of the findings from Study 007, the strength of the MBS co-primary endpoint analysis from Study 006, and the known analgesic effects of NSAIDs as a class, as the basis of her recommendation. Dr. Livezey also comments on supportive secondary endpoint analyses that suggest less use of rescue medication and higher rates of 24-hour sustained pain freedom in DFN-15-treated patients compared to placebo-treated patients; however, these findings are only considered exploratory and are not considered as support for the efficacy of this product in this summary review.

Efficacy by subgroups

Dr. Ling performed analyses of the treatment effect across subgroups for both Studies 006 and 007, and concludes that the efficacy trends observed in the primary efficacy analyses appeared to be similar across all subgroups (age, gender, and race); however, no definitive conclusions can be made based on the small sample sizes for these respective comparisons.

Efficacy Conclusions

The applicant has provided evidence to support efficacy of DFN-15 for the acute treatment of migraine with and without aura in adults based on the results from two identically designed adequate and well-controlled investigations (Studies 006 and 007). Both studies demonstrated statistically significantly greater proportions of DFN-15-treated patients who were MBS-free at 2 hours post-dose, relative to placebo-treated patients. Study 007 demonstrated a statistically significantly greater proportion of DFN-15-treated patients who were pain-free at 2 hours post-dose, relative to placebo-treated patients; however, Study 006 only demonstrated a strong numerical trend towards efficacy on this endpoint that was not statistically significant. These results were consistent with additional sensitivity analyses, including a worst-case scenario regarding the handling of missing data, that were performed by Dr. Ling. The results of the analyses of the secondary efficacy endpoints from both trials, although generally consistent with the primary efficacy results, are only considered exploratory and are therefore not capable of supporting the efficacy of DFN-15.

The efficacy data provided in this application support approval of DFN-15 (a dose of 120 mg in a 24-hour period) for the proposed indication, despite the lack of a statistically significant result on the pain-freedom endpoint in Study 006.

The goal of an acute treatment for migraine is to eliminate both migraine pain and migraine associated symptoms (nausea, photophobia, and/or phonophobia). Both Studies 006 and 007 demonstrated that a greater proportion of DFN-15-treated patients had a resolution of their self-identified MBS at 2 hours post-dose, compared to placebo-treated patients. These results establish that DFN-15 is effective for the acute treatment of migraine associated symptoms (i.e., that the observed treatment effect is not solely analgesic in nature). Study 007 also demonstrated a highly statistically significant effect of DFN-15 on migraine pain at 2 hours post-dose ($p<0.001$), with a near-statistically significant result on this endpoint in Study 006 ($p=0.076$). This finding is in the context of the fact that NSAIDs as a class are established to

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be effective for the treatment of pain in a variety of conditions and the LD, Celebrex, has an indication for the acute treatment of pain. Additionally, other NSAIDs have been approved for the acute treatment of migraine. Ultimately, the established effect of DFN-15 on migraine associated symptoms, along with the strength of the pain-freedom result from Study 007 in the setting of a drug from a class with known analgesic properties, support its efficacy for the acute treatment of migraine without the need to replicate these findings in an additional efficacy trial.

8. Safety

Dr. Viveca Livezey conducted the clinical safety review of this application.

As discussed by Dr. Livezey, the applicant provided safety data from Studies 006 and 007 and is relying on the LD (Celebrex) to support the long-term safety of this product. She reports that 815 patients were exposed to at least one dose of DFN-15 in the current development program. Five hundred seventy-four patients were exposed to at least one dose of DFN-15 in DB1 and a total of 815 patients were exposed to at least one dose when considering DB1 and DB2, collectively.

Dr. Livezey reports that there were no deaths in the development program. No serious adverse events (SAEs) were reported in the Phase 1 and 2 studies, and there were 6 SAEs reported in the Phase 3 studies. None of the SAEs reported seemed to be related to DFN-15. There was a total of 3 patients that received DFN-15 in the controlled efficacy trials that discontinued due to an adverse event (AE). Of these patients, the AEs that were considered possibly related to study drug were urticaria and elevated blood pressure; however, Dr. Livezey concludes, based on her review, that the SAEs and AEs that led to discontinuations in this application do not warrant description in labeling.

Upon review of the treatment-emergent AEs, Dr. Livezey notes that dysgeusia and nausea occurred more commonly in the DFN-15-treated patients as compared to placebo-treated patients. She also notes that the difference between the two groups for nausea is less than 1% and recommends that only the AE of dysgeusia is described in labeling, as it occurs at a rate of 3% and higher than placebo. Refer to Table 5 below.

Table 5: Studies 006 and 007-Treatment Emergent Adverse Events Greater Than or Equal to 1% (source: Dr. Livezey's review Table 34)

System Organ Class	AE Term	DFN-15 120 mg	Placebo
		N=574	N=565
Gastrointestinal	Nausea	13 (2.3%)	10 (1.8%)
Nervous system disorders	Dysgeusia	17 (3.0%)	7 (1.2%)

Safety Conclusions

There are no safety issues that preclude approval.

Reference ID: 4603588

The safety profile of DFN-15 described in labeling will predominantly be derived from the Celebrex PI with the addition of the AE of dysgeusia identified in the clinical trials conducted with DFN-15. The Celebrex PI includes boxed warnings regarding the risk of serious cardiovascular and gastrointestinal events, as well as Warnings and Precautions sections pertaining to hepatoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, premature closure of fetal ductus arteriosus, and hematologic toxicity. A Warning and Precaution section for medication overuse headache should also be included, as this risk is associated with overuse of NSAIDS for the acute treatment of migraine.

9. Pediatrics

DFN-15 was discussed at a Pediatric Review Committee (PeRC) meeting on March 10, 2020. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in patients 0 to less than 6 years of age (on the basis that such studies are highly impracticable) and a post-approval deferral of such trials in patients 6 to 17 years of age. Please refer to Section 12 of this memo for the required pediatric postmarketing study.

10. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Alfaro states that four clinical sites were inspected in support of this NDA, specifically for Studies 006 and 007. Dr. Alfaro reports that there was under-reporting of non-serious adverse events and concomitant medications at one site for a small percentage of patients. Otherwise, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Beverly Weitzman was the primary reviewer and Dr. Briana Rider was team leader for the DMEPA review. DMEPA concludes that the final agreed-upon PI, container labels, and carton labeling are acceptable.

Dr. Weitzman reviewed the proposed proprietary name, Elyxyb, and concludes that this name is acceptable.

11. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

12. Postmarketing Recommendations

Postmarketing Requirement (PMR)

Reference ID: 4603532

PMR-1 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evaluate Elyxyb oral solution compared to placebo in the treatment of acute migraine in pediatric in pediatric patients ages 6 to less than 18 years. This study should include an initial blinded placebo run-in period to identify placebo non-responders for enrollment into the efficacy portion of the trial. The efficacy study must be designed to show superiority of Elyxyb over placebo and should be submitted as a special protocol assessment (SPA).

Reference ID: 4603532

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/

HEATHER D FITTER
05/05/2020 02:09:54 PM

NICHOLAS A KOZAUER
05/05/2020 02:15:03 PM