ELYXYB- celecoxib solution
Dr. Reddy's Laboratories, Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELYXYB safely and effectively. See full prescribing information for ELYXYB.

ELYXYB (celecoxib) oral solution
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)**
- **ELYXYB is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

INDICATIONS AND USAGE

ELYXYB is a nonsteroidal anti-inflammatory drug indicated for the acute treatment of migraine with or without aura in adults (1)

Limitations of Use

ELYXYB is not indicated for the preventive treatment of migraine. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of ELYXYB is 120 mg taken orally, with or without food. (2.1)
- The maximum dosage in a 24-hour period is 120 mg. (2.1)
- Use ELYXYB for the fewest number of days per month, as needed. (2.1)
- Hepatic Impairment: The recommended and maximum dose is 60 mg (2.4 mL) in patients with moderate hepatic impairment (Child-Pugh Class B) (2.2, 8.6, 12.3)
- Poor Metabolizers of CYP2C9 Substrates: The recommended and maximum dose is 60 mg (2.4 mL) in patients who are known or suspected to be CYP2C9 poor metabolizers (2.3, 8.8, 12.5)

DOSAGE FORMS AND STRENGTHS

Oral solution, 120 mg/4.8 mL (25 mg/mL) (3)

CONTRAINDICATIONS

- Known hypersensitivity to celecoxib, any components of the drug product, or sulfonamides (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of ELYXYB in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ELYXYB in patients with severe renal impairment unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: ELYXYB is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue ELYXYB at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Medication Overuse Headache: Detoxification may be necessary (5.10)

- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

ADVERSE REACTIONS

Most common adverse reaction (at least 3% and greater than placebo) is dysgeusia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Promius Pharma, LLC. at 1-888-966-8766 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking ELYXYB with drugs that interfere with hemostasis. Concomitant use of ELYXYB and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with ELYXYB may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with ELYXYB in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with ELYXYB can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks of gestation (5.11, 8.1)
- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of ELYXYB in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use *[see Warnings and Precautions (5.1)]*.**
- **ELYXYB is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events *[see Warnings and Precautions (5.2)]*.**

1. INDICATIONS AND USAGE

ELYXYB is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use

ELYXYB is not indicated for the preventive treatment of migraine.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ELYXYB is 120 mg taken orally, with or without food *[see Clinical Pharmacology (*12.3*)]*.

The maximum dosage in a 24-hour period is 120 mg. The safety and effectiveness of a second dose in a 24-hour period have not been established.

Use ELYXYB for the fewest number of days per month, as needed.

2.2 Dosage Modification in Patients with Hepatic Impairment

The recommended and maximum dose in patients with moderate hepatic impairment (Child-Pugh Class B) is 60 mg (2.4 mL) *[see Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*. A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device. Use of ELYXYB in patients with severe hepatic impairment is not recommended.

2.3 Dosage Modification in CYP2C9 Poor Metabolizers

The recommended and maximum dose in patients who are known or suspected to be CYP2C9 poor metabolizers is 60 mg (2.4 mL) *[see Use in Specific Populations (8.8)* and *Clinical Pharmacology (12.5)]*. A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

3. DOSAGE FORMS AND STRENGTHS

Dosage form: Clear colorless oral solution

Strength: 120 mg/4.8 mL (25 mg/mL)

4. CONTRAINDICATIONS

ELYXYB is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to celecoxib, any components of the drug product *[see Warnings and Precautions (5.7, 5.9)]*.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients *[see Warnings and Precautions (5.7, 5.8)]*.
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]*.
- In patients who have demonstrated allergic-type reactions to sulfonamides. *[see Warnings and Precautions (5.7)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In a trial with celecoxib capsules, there was about a threefold increased risk of the composite endpoint of cardiovascular death, MI, or stroke for the celecoxib 400 mg twice daily and celecoxib 200 mg twice daily treatment arms compared to placebo. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use ELYXYB for the fewest number of days per month as needed, based on individual treatment goals. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ELYXYB, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions(5.2)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID administered in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs, including ELYXYB, are contraindicated in the setting of CABG *[see Contraindications (4)]* .

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100

person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of ELYXYB in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ELYXYB is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including ELYXYB, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with celecoxib. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation.

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with severe liver impairment and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue ELYXYB until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs, including ELYXYB.

In controlled clinical trials of celecoxib capsules, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., nausea, fatigue, pruritus, jaundice, right upper quadrant tenderness, and/or flu-like symptoms),

discontinue ELYXYB immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including ELYXYB, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDS, including ELYXYB, with caution in patients with hypertension. Monitor blood pressure (BP) during the initiation of ELYXYB treatment and throughout the course of therapy.

Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]*.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ELYXYB may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) *[see Drug Interactions (7)]*.

In a clinical study, the cumulative rates at 9 months of peripheral edema in patients on celecoxib capsules 400 mg twice daily, ibuprofen 800 mg three times daily, and diclofenac 75 mg twice daily were 4.5%, 6.9%, and 4.7%, respectively.

Avoid the use of ELYXYB in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ELYXYB is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs, including celecoxib, the active ingredient in ELYXYB, has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors or the ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of celecoxib in patients with severe renal impairment. The renal effects of celecoxib may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating ELYXYB. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of ELYXYB *[see Drug Interactions (7)]*. ELYXYB is not recommended in patients with severe renal impairment.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these

effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. Celecoxib is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people *[see Contraindications (4) and Warnings and Precautions (5.8)]*.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ELYXYB is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]*. When ELYXYB is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

Serious skin reactions have occurred following treatment with celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of ELYXYB at the first appearance of skin rash or any other sign of hypersensitivity. ELYXYB is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

5.10 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, nonsteroidal anti-inflammatory drugs or combination of these drugs for 10 or more days per month), including ELYXYB, may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.11 Premature Closure of Fetal Ductus Arteriosus

ELYXYB may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including ELYXYB, in pregnant women starting at 30 weeks of gestation (third trimester) *[see Use in Specific Populations (8.1)]*.

5.12 Hematological Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with ELYXYB has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

In controlled clinical trials of celecoxib capsules, the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with ELYXYB should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs, including ELYXYB, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]*.

5.13 Masking of Inflammation and Fever

The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID, including ELYXYB, treatment with a CBC and a chemistry profile periodically *[see Warnings and Precautions (5.2, 5.3, 5.6)]*.

In controlled clinical trials with celecoxib capsules, elevated BUN occurred more frequently in patients receiving celecoxib compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.15 Disseminated Intravascular Coagulation (DIC)

ELYXYB is not indicated in pediatric patients or for the treatment of juvenile rheumatoid arthritis (JRA). Disseminated intravascular coagulation has occurred with use of celecoxib capsules in pediatric patients with systemic onset JRA, which required monitoring for signs and symptoms of abnormal clotting or bleeding.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.1)]*
- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.5)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.6)]*
- Anaphylactic Reactions *[see Warnings and Precautions (5.7)]*
- Exacerbation of Asthma Related to Aspirin Sensitivity *[see Warnings and Precautions (5.8)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.9)]*
- Medication Overuse Headache *[see Warnings and Precautions (5.10)]*
- Premature Closure of Fetal Ductus Arteriosus *[see Warnings and Precautions (5.11)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ELYXYB was evaluated in 815 patients who received at least one dose of ELYXYB in two, randomized, double-blind, placebo-controlled trials (Study 1 and 2) in adult patients with migraine [see *Clinical Studies (14)*].

The most common (at least 2% of patients who received ELYXYB and greater than placebo) adverse reaction in Study 1 and Study 2 was dysgeusia, which occurred in 3% of patients who received ELYXB compared to 1% of patients who received placebo.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of celecoxib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to

reliably estimate their frequency or establish a causal relation ship to drug exposure.

Cardiovascular: Vasculitis, deep venous thrombosis

General: Anaphylactic reaction, angioedema

Liver and biliary: Liver necrosis, hepatitis, jaundice, hepatic failure

Hemic and lymphatic: Agranulocytosis, aplastic anemia, pancytopenia, leucopenia

Metabolic: Hypoglycemia, hyponatremia

Nervous: Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage

Renal: Interstitial nephritis

7. DRUG INTERACTIONS

See **Table 1** for clinically significant drug interactions with celecoxib.

Table 1: Clinically Significant Drug Interactions with Celecoxib

Drugs That Interfere with Hemostasis	
Clinical Impact	• Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of celecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention	Monitor patients with concomitant use of ELYXYB with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding *[see Warnings and Precautions (5.12)]*.
Aspirin	
Clinical Impact	• In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.2)]*. • In two studies in healthy volunteers and in patients with established heart disease respectively, celecoxib (200 mg to 400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100 mg to 325 mg).
Intervention	Concomitant use of ELYXYB and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.12)]*. ELYXYB is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact	• NSAIDs may diminish the antihypertensive effect of ACE inhibiters, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Intervention	• During concomitant use of ELYXYB and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of ELYXYB and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.6)]*.When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact	Clinical studies, as well as postmarketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention	During concomitant use of ELYXYB with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions(5.6)*].
Digoxin	
Clinical Impact	The concomitant use of celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention	During concomitant use of ELYXYB and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention	During concomitant use of ELYXYB and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Celecoxib has no effect on methotrexate pharmacokinetics.
Intervention	During concomitant use of ELYXYB and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact	Concomitant use of celecoxib and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention	During concomitant use of ELYXYB and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact	Concomitant use of celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity *[see Warnings and Precautions (5.2)]*.
Intervention	The concomitant use of ELYXYB with other NSAIDs or salicylates is not recommended.
Pemetrexed	
	Concomitant use of celecoxib and pemetrexed may increase the risk of

Clinical Impact	pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention	• During concomitant use of ELYXYB and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal, and GI toxicity. • NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. • In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
CYP2C9 Inhibitors or inducers	
Clinical Impact	Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of ELYXYB with drugs that are known to inhibit CYP2C9 (e.g., fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of ELYXYB.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing ELYXYB. A dosage adjustment may be warranted when ELYXYB is administered with CYP2C9 inhibitors or inducers.
CYP2D6 substrates	
Clinical Impact	I*n vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6 (e.g., atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing ELYXYB. A dosage adjustment may be warranted when ELYXYB is administered with CYP2D6 substrates.
Corticosteroids	
Clinical Impact	Concomitant use of corticosteroids with celecoxib may increase the risk of GI ulceration or bleeding.
Intervention	Monitor patients with concomitant use of ELYXYB with corticosteroids for signs of bleeding *[see Warnings and Precautions (5.2)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including celecoxib, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including ELYXYB, in pregnant women starting at 30 weeks of gestation.

There are no adequate and well-controlled studies of celecoxib in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal studies, administration of celecoxib during pregnancy resulted in adverse effects on development, including increases in embryonic death and fetal malformations, at doses or maternal plasma drug exposures greater than those used clinically [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular

permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss.

In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of celecoxib during labor or delivery. In animal studies, NSAIDs, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

The available data do not establish the presence or absence of developmental toxicity related to the use of celecoxib.

Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus.

Animal data

Administration of celecoxib to rats during early embryonic development resulted in increased pre- and postimplantation loss at oral doses ≥50 mg/kg/day, which was associated with plasma exposure (AUC) approximately 20 times that in humans at the maximum recommended dose (MRHD) of 120 mg/day.

Administration of celecoxib to pregnant rats throughout the period of organogenesis resulted in increased incidences of a specific fetal malformation (diaphragmatic hernia) at oral doses ≥30 mg/kg/day, associated with plasma exposure (AUC) approximately 20 times that in humans at the MRHD.

Administration of celecoxib to pregnant rabbits throughout organogenesis produced increased incidences of fetal visceral (ventricular septal defects) and skeletal malformations at oral doses ≥150 mg/kg/day, associated with maternal plasma AUC approximately 7 times that in humans at the MRHD.

Celecoxib produced no evidence of delayed labor or parturition in rats at oral doses up to 100 mg/kg/day, which was associated with maternal plasma AUC approximately 25 times that in humans at the MRHD.

8.2 Lactation

Risk Summary

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of celecoxib in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants who were 17 and 22 months of age did not show any adverse events. There is no information available regarding the effects of celecoxib on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ELYXYB and any potential adverse effects on the breastfed infant from the celecoxib or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including ELYXYB, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including ELYXYB, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Disseminated intravascular coagulation has occurred in pediatric patients *[see Warnings and Precautions (5.15)]*.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, treat for the fewest number of days per month, as needed, and monitor patients for adverse effects *[see Warning and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)]*.

In the controlled clinical trials for migraine, approximately 70 patients were ≥ 65 years of age. Of the total number of patients who received celecoxib (for indications other than migraine) in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous postmarketing reports of fatal GI events and acute renal failure in the elderly than in younger patients *[see Warnings and Precautions (5.4, 5.6)]*.

8.6 Hepatic Impairment

No dosage adjustment is needed for patients with mild hepatic impairment (Child-Pugh Class A). Reduce the dose of ELYXYB in patients with moderate hepatic impairment (Child-Pugh Class B) *(see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*. The use of ELYXYB in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended.

8.7 Renal Impairment

No dosage adjustment is needed for patients with mild or moderate renal impairment. ELYXYB is not recommended in patients with severe renal impairment *(see Warnings and Precautions (5.6)* and *Clinical Pharmacology (12.3)]*.

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (e.g., warfarin, phenytoin) reduce the dose of ELYXYB *[see Dosage and Administration (*2.3) *and Clinical Pharmacology (12.5)]*.

10. OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

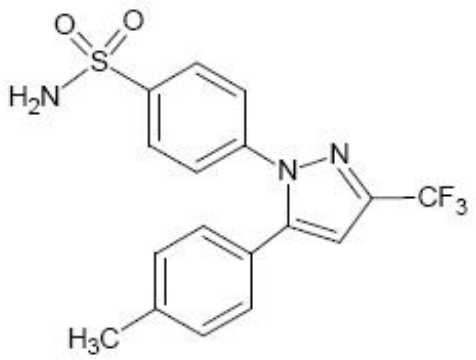
No overdoses of celecoxib were reported during clinical trials. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%), dialysis is unlikely to be useful in overdose.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center.

11. DESCRIPTION

ELYXYB is an oral solution of celecoxib, a nonsteroidal anti-inflammatory drug. Each unit dose of ELYXYB contains 120 mg of celecoxib. Celecoxib is a white or almost white, crystalline or amorphous powder with a pKa of 11. Celecoxib is hydrophobic (log P is 3.0) and practically insoluble in water. Celecoxib is chemically designated as *p*-[5-*p*-tolyl-3-(trifluoromethyl) pyrazol-1-yl] benzenesulfonamide. The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.37. It has the following chemical structure:



The inactive ingredients in ELYXYB include: acesulfame potassium, banana flavor, bubble gum flavor, ethyl alcohol, glycerin, glyceryl monocaprylate, L-menthol, lauroyl polyoxyl-32 glycerides, medium chain triglycerides, monoammonium glycyrrhizinate, peppermint flavor, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, propyl gallate, purified water, and sucralose.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Celecoxib is a nonsteroidal anti-inflammatory drug with analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action by which celecoxib exerts therapeutic effects in migraine patients is not fully understood but may involve inhibition of prostaglandin synthesis, primarily via inhibition of COX-2.

12.2 Pharmacodynamics

Platelets

In clinical trials using normal volunteers, celecoxib at single doses up to 800 mg and multiple doses of

600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time.

Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of celecoxib.

Fluid Retention

Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

12.3 Pharmacokinetics

Celecoxib exhibits a dose-proportional increase in exposure after once daily oral administration of 120 to 240 mg doses (2 times the recommended dosage) of ELYXYB.

Absorption

Following administration of 120 mg of ELYXYB under fasting condition in 24 healthy subjects, the median time to peak plasma levels (i.e., T_{max}) of celecoxib was 1 hour (range 0.67 to 3.00).

Food Effect

When ELYXYB was taken with a high-fat meal, the median time to peak plasma levels (i.e., T_{max}) was delayed by 2 hours with an approximately 50% decrease in C_{max} and no change in total absorption (i.e., AUC) compared to fasting conditions. However, in Study 1 and Study 2, ELYXYB was administered without regard to food *[see Dosage and Administration (2.1), Clinical Studies (14)]*.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α1-acid glycoprotein. The apparent volume of distribution following single dose administration of ELYXYB at fasting state is (Vz/F) is approximately 288 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Metabolism

Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid, and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. The mean apparent elimination t½ of celecoxib from ELYXYB was approximately 6 hours independent of dosing condition and similar to that observed for Celebrex under fed conditions.

Specific Populations:

Geriatric

At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC

compared to the younger subjects for celecoxib oral capsules. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary.

Race

Meta-analysis of pharmacokinetic studies conducted using celecoxib oral capsules has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ELYXYB has not been evaluated. A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment conducted using celecoxib oral capsule has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects *[seeDosage and Administration (2.2) and Use in Specific Populations (8.6)]*. . Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment

In a cross-study comparison done for celecoxib oral capsules, celecoxib AUC was approximately 40% lower in patients with chronic renal impairment (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal impairment have not been studied *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19, or 3A4.

In vivo studies have shown the following:

Aspirin

When NSAIDs were administered with aspirin, the protein binding of NSAIDs was reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known *[see Drug Interactions (7)]*.

Lithium

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with celecoxib 200 mg oral capsule twice daily as compared to subjects receiving lithium alone *[see Drug Interactions (7)]*.

Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole *[see Drug Interactions (7)]*.

Other Drugs

The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, phenytoin, and tolbutamide have been studied *in vivo* using celecoxib oral capsules and clinically important interactions have not been found.

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to

subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. *[see Dosage and Administration (2.3) and Use in Specific Populations (8.8)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Celecoxib was not carcinogenic when administered orally for two years to rats at oral doses up to 200 mg/kg for males and 10 mg/kg for females (associated with plasma exposures (AUC) approximately 14 and 7 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 120 mg/day) or in mice at oral doses up to 25 mg/kg for males and 50 mg/kg for females (associated with plasma AUCs approximately 4 times in humans at the MRHD.

Mutagenesis

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Impairment of Fertility

Administration of celecoxib to male and female rats prior to and during mating and continuing in females through implantation had no effect on fertility or male reproductive function at oral doses up to 600 mg/kg/day, which were associated with plasma AUCs approximately 40 times that in humans at the MRHD. Increased implantation loss was observed at doses ≥50 mg/kg/day, which was associated with plasma AUC approximately 20 times that in humans at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules were seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

14. CLINICAL STUDIES

14.1 Migraine

The efficacy of ELYXYB for the acute treatment of migraine with or without aura was demonstrated in two randomized, double-blind, placebo-controlled clinical trials [Study 1 (NCT03009019) and Study 2 (NCT03006276)]. In Study 1, patients were randomized to receive ELYXYB 120 mg (n=316) or placebo (n=315); in Study 2, patients were also randomized to receive ELYXYB 120 mg (n=311) or placebo (n=311). In both studies, patients were instructed to treat a migraine with moderate to severe pain intensity.

Patients enrolled in the trials were predominantly female (86%) and White (74%), with a mean age of 40.6 years (range 18 to 75 years).

The primary efficacy analyses were conducted in patients who treated a migraine with moderate to severe pain. The efficacy of ELYXYB was established by an effect on pain freedom at 2 hours post-dose and most bothersome symptom (MBS) freedom at 2 hours post-dose. Pain freedom was defined as a reduction of moderate or severe headache pain to no pain, and MBS freedom was defined as the

absence of the self-identified MBS (photophobia, phonophobia, or nausea). Among patients who selected a MBS, the most commonly selected MBS was photophobia (56%), followed by nausea (25%), and phonophobia (18%).

In both studies, the percentage of patients achieving MBS freedom at 2 hours post-dose was significantly greater among patients receiving ELYXYB, compared to those receiving placebo. In Study 2, the percentage of patients achieving headache pain freedom at 2 hours post-dose was significantly greater among patients receiving ELYXYB, compared to those receiving placebo (*see Table 2)*.

Table 2: Migraine Efficacy Endpoints for Study 1 and Study 2

	Study 1		**Study 2**	
	Placebo	**ELYXYB 120 mg**	**Placebo**	**ELYXYB 120 mg**
Pain Free at 2 hours				
N	273	284	271	279
% Responders	25.3	32.4	21.0	35.1
Difference from placebo (%)		7		14
p-value		0.076[a]		<0.001
Most Bothersome Symptom Free at 2 hours				
N	234	245	237	236
% Responders	44.4	58.0	43.9	56.8
Difference from placebo (%)		14		13
p-value		0.003		0.006

[a]Not statistically significant

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ELYXYB (celecoxib) oral solution, 120 mg/4.8 mL (25 mg/mL) is a clear colorless oral solution supplied in a disposable glass bottle with a child resistant cap.

Each carton (NDC 43598-866-09) contains nine (9) glass bottles, a Full Prescribing Information, Medication Guide, and Instructions for Use

16.2 Storage and Handling

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Do not refrigerate or freeze.

Unused portion should be discarded immediately after use.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

For patients who are prescribed the recommended dosage of 120 mg, instruct them to drink the entire amount of ELYXYB directly from the bottle.

For patients who are prescribed the reduced dosage (i.e., patients with moderate hepatic impairment or CYP2C9 poor metabolizers), instruct them to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform these patients that oral dosing syringes may be obtained from their pharmacy and that a household teaspoon is not an accurate measuring device. Instruct these patients to discard the unused portion of ELYXYB.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop ELYXYB and seek immediate medical therapy [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions

Advise patients to stop ELYXYB immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9)*].

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month, including ELYXYB, may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary). Instruct patients to contact their healthcare provider if the frequency of their migraines increases; withdrawal of ELYXYB may be necessary [see *Warnings and*

Precautions (5.10)].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including ELYXYB, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of ELYXYB and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [see *Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of ELYXYB with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with ELYXYB until they talk to their healthcare provider [*see Drug Interactions (7)*].

ELYXYB is a trademark of Dr. Reddy's Laboratories Limited

Manufactured for: Dr. Reddy's Laboratories Limited, 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Telangana 500034, India

Medication Guide
ELYXYB (ee-lix'-ib)
(celecoxib) oral solution

What is the most important information I should know about ELYXYB?

ELYXYB contains celecoxib (a non-steroidal anti-inflammatory drug or NSAID). NSAIDs, including ELYXYB, can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take ELYXYB right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs, including ELYXYB, after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "antiplatelet drugs", "anticoagulants", "SSRIs" or "SNRIs"

- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

ELYXYB should only be used:

- exactly as prescribed
- for the shortest time needed

What is ELYXYB?

ELYXYB is a prescription medicine used for the acute treatment of migraine attacks with or without aura in adults.

- ELYXYB is not used as a preventive treatment of migraine.
- It is not known if ELYXYB is safe and effective in children.

Who should not take ELYXYB?

Do not take ELYXYB:

- if you are allergic to celecoxib or any of the ingredients in ELYXYB. See the end of this Medication Guide for a complete list of ingredients in ELYXYB.
- If you are allergic to sulfonamides.
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking ELYXYB, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- have a history of stomach ulcer or bleeding in your stomach or intestines.
- have heart disease or risk factors that increase your chance of getting heart disease.
- have high blood pressure.
- have asthma .
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking ELYXYB during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy**
- are breastfeeding or plan to breast feed**.** ELYXYB may pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you take ELYXYB.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs , including ELYXYB, and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

How should I take ELYXYB?

See the detailed "Instructions for Use" on how to take ELYXYB solution.

- Take ELYXYB exactly as your healthcare provider tells you to take it.
- Take ELYXYB by mouth with or without food.
- Do not take more than one dose in a 24-hour period.
- Use ELYXYB for the fewest number of days a month, as needed.

What are the possible side effects of ELYXYB?

ELYXYB can cause serious side effects, including:

See "What is the most important information I should know about ELYXYB?

- liver problems including liver failure
- new or worse high blood pressure
- heart failure
- kidney problems including kidney failure
- life-threatening allergic reactions
- asthma attacks in people who have asthma
- life-threatening skin reactions
- medication overuse headaches. Some people who use too much ELYXYB may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with ELYXYB.
- low red blood cells (anemia)
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking ELYXYB and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much ELYXYB, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of ELYXYB

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELYXYB for a condition for which it was not prescribed. Do not give ELYXYB to other people, even if they have the same symptoms that you have. It may harm them.
If you would like more information about ELYXYB, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ELYXYB that is written for health professionals.

Manufactured for: Dr. Reddy's Laboratories Limited.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 5/2020

Instructions For Use

ELYXYB (ee-lix'-ib)
(celecoxib)
oral solution
25 mg/mL

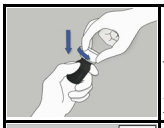
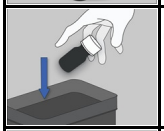
Read this Instructions for Use before you start taking ELYXYB and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment. Take ELYXYB exactly how your healthcare provider tells you to.

If your healthcare provider has prescribed 120 mg of ELYXYB, take all of the medicine in the bottle as described below in **Instructions-1.**

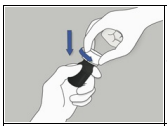
If your healthcare provider has prescribed 60 mg of ELYXYB, take 2.4 mL of the medicine, as described in **Instructions-2**. You will need a dosing syringe from the pharmacy to give the right amount of medicine.

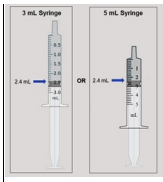
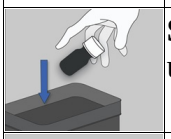
Do not use a household teaspoon to measure ELYXYB.

Instructions-1 (Full dose of 120 mg)

	**Step 1:** When you need to take ELYXYB, push down the cap and turn it to the left (counterclockwise) to open it.
	**Step 2**: When taking 120 mg of ELYXYB, drink it directly from the bottle. Hold the bottle upside down for 10 seconds to make sure the full amount of medicine is taken.
	**Step 3:** Close the bottle by turning the cap to the right (clockwise) right away after drinking the medicine.
	**Step 4:** Throw away (discard) the bottle.
	**Step 5:** After you take ELYXYB, you may drink up to 8 ounces (240 mL) of water.

Instructions-2 (50 % reduced dose of 60 mg)

	**Step 1**: When you need to take ELYXYB, push down the cap and turn it to the left (counterclockwise) to open it.

	**Step 2:** Use an oral dosing syringe (3 mL or 5 mL) from your pharmacy to withdraw 2.4 mL of ELYXYB. Insert the syringe through ELYXYB bottle opening and draw up 2.4 mL of ELYXYB directly from the bottle into the syringe. This 2.4 mL will be your 60 mg dose. **Note: Do not use a household teaspoon to measure ELYXYB.**
Step 3: Place the 2.4 mL of the ELYXYB that is in the dosing syringe in your mouth and swallow it right away.	
	**Step 4:** Close the bottle tightly by turning the cap to the right (clockwise) right away after taking the correct dose of ELYXYB. **Note: Do not store the bottle to reuse the remaining medicine.**
	**Step 5:** Throw away (discard) the bottle with the unused ELYXYB.
	**Step 6**: After you take ELYXYB, you may drink up to 8 ounces (240 mL) of water.

This Instructions has been approved by the U.S. Food and Drug for Use Administration.

Approved: 5/2020

PRINCIPAL DISPLAY PANEL - Bottle Label

PRINCIPAL DISPLAY PANEL - Carton Label

ELYXYB

celecoxib solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43598-866
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CELECOXIB (UNII: JCX84Q7J1L) (CELECOXIB - UNII:JCX84Q7J1L)	CELECOXIB	25 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43598-866-09	9 in 1 CARTON	10/05/2020	
1	NDC:43598-866-04	4.8 mL in 1 BOTTLE, UNIT-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212157	10/05/2020	

Labeler - Dr. Reddy’s Laboratories, Inc (802315887)

Registrant - Dr. Reddy's Laboratories, Ltd. (862179079)

Revised: 5/2020 Dr. Reddy’s Laboratories, Inc