ELYXYB™ (Celecoxib) oral solution

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.**
- **ELYXYB is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**
- **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.**

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Cardiovascular Thrombotic Events

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Gastrointestinal Bleeding, Ulceration, and Perforation

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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.

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
- 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
- In the setting of coronary artery bypass graft (CABG)
- In patients who have demonstrated allergic-type reactions to sulfonamides

WARNINGS AND PRECAUTIONS

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.

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.

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.

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 post marketing 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.

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.

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.

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]).

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.

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. 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.

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.

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. When ELYXYB is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

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.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ELYXYB. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ELYXYB and evaluate the patient immediately.

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.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including ELYXYB, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ELYXYB, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including ELYXYB, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ELYXYB use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ELYXYB treatment extends beyond 48 hours. Discontinue ELYXYB if oligohydramnios occurs and follow up according to clinical practice.

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.

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.

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.

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.

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.

ADVERSE REACTIONS

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

- Cardiovascular Thrombotic Events
- GI Bleeding, Ulceration, and Perforation
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions
- Exacerbation of Asthma Related to Aspirin Sensitivity
- Serious Skin Reactions
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Medication Overuse Headache
- Fetal Toxicity
- Hematologic Toxicity

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.

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 ELYXYB compared to 1% of patients who received placebo.

Post marketing 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 relationship 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