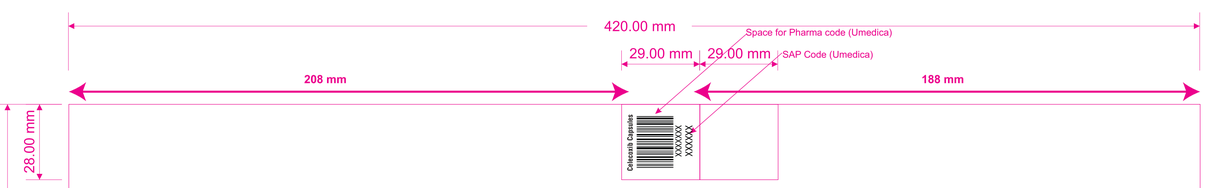

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CELECOXIB CAPSULES safely and effectively. See full prescribing information for CELECOXIB CAPSULES.

CELECOXIB capsules, for oral use
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)**
- **Celecoxib capsules are 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)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.9) 11/2024

INDICATIONS AND USAGE

Celecoxib Capsules is a nonsteroidal anti-inflammatory drug indicated for:
- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Acute Pain (AP) (1.5)
- Primary Dysmenorrhea (PD) (1.6)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2.1)
- OA: 200 mg once daily or 100 mg twice daily. (2.2, 14.1)
- RA: 100 to 200 mg twice daily. (2.3, 14.2)
- JRA: 50 mg twice daily in patients 10 kg to 25 kg; 100 mg twice daily in patients more than 25 kg. (2.4, 14.3)
- AS: 200 mg/day; dose may be given as 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit. (2.5,14.4)
- AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed. (2.6, 14.5)

Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). (2.7, 8.6, 12.3)

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers. (2.7, 8.8, 12.3)

DOSAGE FORMS AND STRENGTHS

Celecoxib capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to celecoxib, or 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 celecoxib capsules 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 celecoxib capsules in patients with advanced renal disease 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: celecoxib capsules are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue celecoxib capsules at first appearance of skin rash or other signs of hypersensitivity. (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically. (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including celecoxib capsule, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (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 reactions in arthritis trials (>2% and >placebo) are: abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Umedica Laboratories USA Inc. at 1-855-288-5777 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]): Monitor patients for bleeding who are concomitantly taking celecoxib capsules with drugs that interfere with hemostasis. Concomitant use of celecoxib capsules and analgesic doses of aspirin is not generally recommended. (7)
- Angiotensin converting enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta- Blockers: Concomitant use with celecoxib capsules may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
- ACE Inhibitors and ARBs: Concomitant use with celecoxib capsules 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 celecoxib capsules can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)

USE IN SPECIFIC POPULATIONS

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of celecoxib capsules in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2025

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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)*).**
- **Celecoxib capsules are 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

Celecoxib capsules are indicated

1.1 Osteoarthritis (OA)

For the management of the signs and symptoms of OA (*see Clinical Studies (14.1)*).

1.2 Rheumatoid Arthritis (RA)

For the management of the signs and symptoms of RA (*see Clinical Studies (14.2)*).

1.3 Juvenile Rheumatoid Arthritis (JRA)

For the management of the signs and symptoms of JRA in patients 2 years and older (*see Clinical Studies (14.3)*).

1.4 Ankylosing Spondylitis (AS)

For the management of the signs and symptoms of AS (*see Clinical Studies (14.4)*).

1.5 Acute Pain

For the management of acute pain in adults (*see Clinical Studies (14.5)*).

1.6 Primary Dysmenorrhea

For the management of primary dysmenorrhea (*See Clinical Studies (14.5)*).

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of celecoxib capsules and other treatment options before deciding to use celecoxib capsules. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (*See Warnings and Precautions (5)*).

These doses can be given without regard to timing of meals.

2.2 Osteoarthritis

For OA, the dosage is 200 mg per day administered as a single dose or as 100 mg twice daily.

2.3 Rheumatoid Arthritis

For RA, the dosage is 100 mg to 200 mg twice daily.

2.4 Juvenile Rheumatoid Arthritis

For JRA, the dosage for pediatric patients (age 2 years and older) is based on weight. For patients ≥10 kg to <25 kg the recommended dose is 50 mg twice daily; for patients ≥25 kg the recommended dose is 100 mg twice daily.

For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce. The entire capsule contents should be slowly emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The celecoxib capsule contents on applesauce are stable for up to 6 hours when refrigerated conditions (2°C-8°C (36°F-46°F)).

2.5 Ankylosing Spondylitis

For AS, the dosage of celecoxib capsules is 200 mg daily in single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

2.6 Management of Acute Pain and Treatment of Primary Dysmenorrhea

For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage 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 twice daily as needed.

2.7 Special Populations

Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of celecoxib capsules in patients with severe hepatic impairment is not recommended (*see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)*).

Poor Metabolizers of CYP2C9 Substrates

OA: 200 mg once daily or 100 mg twice daily. (2.2, 14.1)
RA: 100 to 200 mg twice daily. (2.3, 14.2)
JRA: 50 mg twice daily in patients 10 kg to 25 kg; 100 mg twice daily in patients more than 25 kg. (2.4, 14.3)
AS: 200 mg/day; dose may be given as 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit. (2.5,14.4)
AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed. (2.6, 14.5)

Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). (2.7, 8.6, 12.3)

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers. (2.7, 8.8, 12.3)

Celecoxib capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)

3. DOSAGE FORMS AND STRENGTHS

Celecoxib capsules:
50 mg white to white opaque hard gelatin capsules, imprinted with 'CEL' on cap & 50 mg on body in black ink.
100 mg white to white opaque hard gelatin capsules, imprinted with 'CEL' on cap & 100 mg on body in black ink.
200 mg white to white opaque hard gelatin capsules, imprinted with 'CEL' on cap & 200 mg on body in black ink.
400 mg white to white opaque hard gelatin capsules, imprinted with 'CEL' on cap & 400 mg on body in black ink.

4. CONTRAINDICATIONS

Celecoxib capsules are 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 CABG surgery (*see Warnings and Precautions (5.1)*).
  - Severe hepatic impairment or severe 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-2 (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 conditions appears to be greater in patients known to have CV disease or risk factors for CV disease because, however, patients with known CV disease or risk factors had a higher absolute incidence of thrombotic events, due to their increased baseline risk. 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 the APC (Adenoma Prevention with Celecoxib) trial, there was a threefold increased risk of the composite endpoint of cardiovascular (CV) death, MI, or stroke for celecoxib capsules 400 mg twice daily and celecoxib capsules 200 mg twice daily treatments across compared to placebo. The increases in both cardiovascular deaths and serious placebo-treated patients were nearly due to an increased incidence of myocardial infarction (*see Clinical Studies (14.7.2)*).

A randomized controlled trial entitled the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) was conducted to evaluate the cardiovascular safety of celecoxib 100 mg twice daily or 200 mg twice daily compared to the non-selective NSAIDs naproxen and ibuprofen. Celecoxib 100 mg twice daily was non-inferior to naproxen 375 to 500 mg twice daily and ibuprofen 600 to 800 mg three times daily for the composite endpoint of the Antipatelet Trialists' Collaboration (APTC), which consists of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke (*See Clinical Studies (14.6)*).

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. 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 celecoxib, 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 for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs 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 death, and of cause-related hospitalization for heart failure (CHF) during the first year after well-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 14 per 100 person years in those not treated with NSAIDs. 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 celecoxib capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If celecoxib capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including celecoxib capsules 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 capsules. 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 Gastrointestinal (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 bleeding, compared to patients with neither of 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, anticoagulants, aspirin, or SSRIs; smoking; alcoholism; and advanced age. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore, special care should be paid to those patients in the treatment of elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Complicated upper gastrointestinal ulcer rates were 0.78% at nine months for all patients in the CLAS/GI trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.80% when also taking low-dose ASA (*See Clinical Studies (14.6)*).

Strategies to Minimize the GI Risks in NSAID-treated patients:
- Use the lowest effective dosage for the shortest possible duration.
- 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 a history of GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert to the signs and symptoms of ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue celecoxib capsules 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 [3ULN]) 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 (one to less than three times 3ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

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 capsules and 5% for placebo, and approximately 2% for NSAID-comparators. Discontinuations for abnormal liver tests in these trials included notable elevations of ALT and AST.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), discontinue celecoxib capsules immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including celecoxib capsules, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. 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)*).

See Clinical Studies (14.6, 14.7) for additional blood pressure data for celecoxib capsules.

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Cox-2 and traditional NSAID Trialists' Collaboration meta-analyses of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure (CHF) 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 celecoxib may blunt the CV effects of several therapeutic agents used for treatment of CV events (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) (*see Drug Interactions (7)*).

Avoid the use of celecoxib capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If celecoxib capsules are 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 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 Capsules in patients with advanced renal disease. The risk of further effects of celecoxib capsules treatment on renal function is expected to be minimal in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating celecoxib capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of celecoxib capsules (*see Drug Interactions (7), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)*). Avoid the use of celecoxib capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If celecoxib capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

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 capsules are contraindicated in patients with known hypersensitivity and should be used with caution in patients with a history of hypersensitivity. Celecoxib capsules are contraindicated in patients with aspirin-sensitive asthma. Emergency help should be sought in cases where an anaphylactic reaction occurs.

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 celecoxib capsules inhibit the synthesis of prostaglandins, it may be expected that administration of celecoxib capsules to patients who are contraindicated in patients with this form of aspirin sensitivity may cause bronchospasm or other hypersensitivity reactions. Celecoxib capsules are 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 capsules, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and fixed drug eruption (FDE) which may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE). 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 celecoxib capsules at the first appearance of skin rash or any other sign of hypersensitivity. Celecoxib capsules are contraindicated in patients with previous serious skin reactions to NSAIDs (*see Contraindications (4)*).

5.10 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 celecoxib capsules, initially presenting with fever and rash, accompanied by lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of 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 if rash is not evident. If such signs or symptoms are present, discontinue Celecoxib Capsules and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

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

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including celecoxib Capsules, 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 in as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose; duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the reproductive risk for inhibition of prostaglandin synthesis has been observed in animal studies, the generalizability of certain reported risks to the full term infant exposed to NSAIDs through maternal use is uncertain.

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving celecoxib capsules and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib and placebo groups were dyspepsia and abdominal pain (pooled data) and the rate of discontinuation was 0.8% and 0.7% of celecoxib patients, respectively). Among patients receiving placebo, 0.8% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

adverse reactions for which these differences in patients treated with celecoxib capsules were greater as compared to the arthritis pre-marketing trials were as follows:

	Celecoxib (400 to 800 mg daily) N = 2285	Placebo N = 1303
Diarrhea	10.5%	7.0%
Gastroesophageal reflux disease	4.7%	3.3%
Nausea	4.2%	3.2%
Vomiting	3.2%	2.1%
Dyspepsia	2.8%	1.6%
Hypertension	12.5%	9.8%
Nasopharyngitis	2.1%	0.8%

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking celecoxib capsules, at an incidence greater than placebo in the long-term pooled arthritis clinical trial data, and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders: Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth: Labyrinthitis

Cardiac disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders: Deep vein thrombosis

Reproductive system and breast disorders: Ovarian cyst

Investigations: Blood potassium increased, blood cholesterol increased, blood testosterone decreased

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

8.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of celecoxib capsules. 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: Anaphylactoid reaction, angioedema

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

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

Metabolic: Hypoglycemia

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

Renal: Interstitial nephritis

Skin and Appendage: Erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and fixed drug eruption (FDE)

Vision/Ear and Labyrinth: Tinnitus

Respiratory: Dyspnea, pulmonary edema

Immune: Anaphylaxis

Psychiatric: Confusion, depression, insomnia

Urogenital: Acute renal failure, renal insufficiency, renal failure, dehydration, or hypovolemia, renal failure, hyperkalemia, renal tubular acidosis, hyponatremia

Musculoskeletal: Myalgia, myasthenia, muscle cramps

Hepatic: Cholestasis, hepatitis, liver failure

Nervous System: Aseptic meningitis, dysgeusia, paresthesia, somnolence

Immune: Anaphylaxis

Skin and appendages: Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin eruption, sweating increased

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following adverse reactions have been identified during post approval use of celecoxib capsules: *Cardiovascular:* Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral thrombosis, cardiomyopathy

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

General: Sepsis, sudden death

Liver and biliary: Cholestasis

Hemic and lymphatic: Thrombocytopenia

Nervous: Ataxia, suicide (*see Drug Interactions (7)*)

Renal: Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study (*see Clinical Studies (14.2)*) Hematological Events: The incidence of clinically significant decrease in hemoglobin (>2 g/dL) was lower in patients on celecoxib capsules 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three times daily (1.1%). Discontinuations for anemia were similar for celecoxib capsules, diclofenac, and ibuprofen.

Renal Events: Edema was the most common renal event resulting in withdrawal for celecoxib capsules, at a rate of 0.3% for celecoxib capsules 400 mg twice daily, 0.4% for celecoxib capsules 200 mg twice daily, and 0.8% for diclofenac 75 mg twice daily and ibuprofen 800 mg three times daily. The most commonly occurring (≥0.5%) adverse renal events were hypertension (renal), peripheral edema, cough, nasopharyngitis, abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥0.5%) adverse experiences for rofecoxib capsules were upper respiratory tract infection, sinusitis, and pharyngitis. Edema was the most common renal event resulting in withdrawal (Class 3) for rofecoxib capsules at 0.3 and 0.6 times the rate for celecoxib capsules. There was no substantial difference in effect on growth and development during the course of the 12-week double-blind study. There was no substantial difference in the number of clinical events adjudicated to be thrombotic cardiovascular events between treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 200 JRA patients were treated with celecoxib 6 mg/kg (or up to a maximum of 300 mg) twice daily, or naproxen 7.5 mg/kg (or up to a maximum of 500 mg) twice daily. The incidence of adverse events of clinical importance emerged.

Table 2: Adverse Events Occurring in ≥5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

	All Doses Twice Daily		
System Organ Class / Preferred Term	Celecoxib 3 mg/kg