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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 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)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.9) 11/2024

INDICATIONS AND USAGE

Celecoxib capsules are 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 mg 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 once daily single dose or 100 mg twice daily. If needed it 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)

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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 are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2°C to 8°C/35°F to 45°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
In 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
In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.

In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments [see Use in Specific Populations (8.8) and Clinical Pharmacology (12.5)].

3. DOSAGE FORMS AND STRENGTHS

- 50 mg white to off-white powder filled in size "4" hard gelatin white capsules, with reverse printed white on red band with markings **SG** on cap and **156** on body.
- 100 mg white to off-white powder filled in size "4" hard gelatin white capsules, with reverse printed white on blue band with markings **SG** on cap and **157** on body.
- 200 mg white to off-white powder filled in size "2" hard gelatin white capsules, with reverse printed white on gold band with markings **SG** on cap and **158** on body.
- 400 mg white to off-white powder filled in size "0" hard gelatin white capsules, with reverse printed white on green band with markings **SG** on cap and **159** on body.

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)].
- 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-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 conferred by NSAID use appears to be similar to 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.

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 capsules, 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, 6.1)
- **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 ScieGen Pharmaceuticals, Inc., at 855-724-3436 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. (5.1)
- **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

- **Fertility.** 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: 2/2026

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

In the APC (Adenoma Prevention with Celecoxib) trial, there was about a threefold increased risk of the composite endpoint of cardiovascular death, MI, or stroke for the celecoxib capsules 400 mg twice daily and celecoxib capsules 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 [see Clinical Studies (14.7)].

A randomized controlled trial entitled the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) was conducted to assess the relative cardiovascular thrombotic risk of a COX-2 inhibitor, celecoxib, compared to the non-selective NSAIDs naproxen and ibuprofen. Celecoxib 100 mg twice daily was non-inferior to naproxen 375 mg to 500 mg twice daily and ibuprofen 600 mg to 800 mg three times daily for the composite endpoint of the Antipplatelet 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 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 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 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 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 advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS 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, 3.06% when also taking ASA [see Clinical Studies (14.7)].

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 active GI bleeding, consider alternative 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 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 [ULN]) have been reported in approximately 1% of patients treated with celecoxib capsules 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 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 0.2% of patients taking celecoxib capsules and 0.3% of patients taking placebo had 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 discomfort 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

Celecoxib capsules, 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 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 celecoxib 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 the CLASS study [see Clinical Studies (14.7)], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib capsules 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), 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 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 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 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)].

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 hyperkalemia-hypodaldosteronism 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)].

Seek emergency help if any anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subgroup of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or reactions to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, celecoxib capsules are contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When celecoxib capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the clinical 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. 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, 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 though rash is not evident. If such signs or symptoms are present, discontinue celecoxib capsules and evaluate the patient immediately.

5.11 Fetal Toxicity

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Clinical Impact:	- NSAIDs may diminish the antihypertensive effect of ACE inhibitors, 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 celecoxib capsules and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. - During concomitant use of celecoxib capsules and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function <i>(see Warnings and Precautions (5.6))</i>. - 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 post-marketing 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 celecoxib capsules with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects <i>(see Warnings and Precautions (5.6))</i> .
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 celecoxib capsules and digoxin, monitor patient 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 celecoxib capsules 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 celecoxib capsules and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of celecoxib capsules and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of celecoxib capsules 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, with little or no increase in efficacy <i>(see Warnings and Precautions (5.2))</i> .
Intervention:	The concomitant use of Celecoxib with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of celecoxib capsules and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity <i>(see the pemetrexed prescribing information)</i> .
Intervention:	During concomitant use of celecoxib capsules and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 mL/min 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. Coadministration of celecoxib 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 celecoxib.
Intervention:	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers. <i>(see Clinical Pharmacology (12.3))</i>
CYP2D6 substrates	
Clinical Impact:	<i>In vitro</i> studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an <i>in vivo</i> 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 celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates. <i>(see Clinical Pharmacology (12.3))</i>
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with celecoxib capsules may increase the risk of GI ulceration or bleeding.
Intervention:	Monitor patients with concomitant use of celecoxib capsules with corticosteroids for signs of bleeding <i>(see Warnings and Precautions (5.2))</i> .

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

Use of NSAIDs, including celecoxib capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit the duration of celecoxib capsules use during pregnancy to about 30 and 30 weeks of gestation and avoid celecoxib capsules use at about 30 weeks of gestation and later in pregnancy *(see Clinical Considerations, Data)*.

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including celecoxib capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose (MRHD) of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, rib fusions, sternbrae fusions and sternbrae mishaps) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD (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. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including celecoxib capsules, can cause premature closure of the fetal ductus arteriosus *(see Data)*.

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 30 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If celecoxib capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue celecoxib capsules and follow up according to clinical practice *(see Data)*.

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 capsules. Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days of treatment, although oligohydramnios has been infrequently reported 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 occurred 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 published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae mishaps when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥ 50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for RA). Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in labor and approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg twice daily. The effects of celecoxib on labor and delivery in pregnant women are unknown.

9.2 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 mcg/kg/day 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 17 and 22 months of age did not show any adverse events. Caution should be exercised when celecoxib capsules are administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for celecoxib and any potential adverse effects on the breastfed infant from the celecoxib or from the underlying maternal condition.

9.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including celecoxib capsules, 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 celecoxib capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.

9.4 Pediatric Use

Celecoxib capsules are approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to celecoxib has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs *(see Boxed Warning, Warnings and Precautions (5.5), and Clinical Studies (14.3))*.

The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). When NSAIDs including celecoxib are used in patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests *(see Dosage and Administration (2.4), Warnings and Precautions (5.5), Adverse Reactions (6.1), Animal Toxicology (13.2), Clinical Studies (14.3))*.

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers *(see Poor Metabolizers of CYP2C9 Substrates (8.8))*.

9.5 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, start dosing at the low end of the dosing range, and monitor patients for adverse effects *(see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14))*.

Of the total number of patients who received celecoxib capsules in pre-approved clinical trials, more than 3,300 were 65 to 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, no differences were 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 post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients *(see Warnings and Precautions (5.2, 5.3, 5.6))*.

9.6 Hepatic Impairment

The daily recommended dose of celecoxib capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of celecoxib in patients with severe hepatic impairment is not recommended *(see Dosage and Administration (2.7) and Clinical Pharmacology (12.3))*.

9.7 Renal Impairment

Celecoxib capsules are not recommended in patients with severe renal insufficiency *(see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3))*.

9.8 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 (such as warfarin phenotypic administration studies) starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers *(see Dosage and Administration (2.7) 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 (5.2, 5.4, 5.6))*.

No overdoses of celecoxib were reported during clinical trials. Doses up to 2,400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. 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 overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 grams to 100 grams in adults, 1 gram to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartics 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, alkalization 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 (1-800-222-1222).

11 DESCRIPTION

Celecoxib is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is $C_{17}H_{14}F_3N_4O_2S_2$ and it has the following chemical structure:

Renal Impairment

In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35 mL to 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 insufficiency have not been studied. Similar to other NSAIDs, celecoxib capsules are not recommended in patients with severe renal insufficiency *(see Warnings and Precautions (5.6))*.

Drug Interaction Studies

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

Aspirin

In vivo studies have shown the following:

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin *(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 capsules 200 mg 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, *(see Drug Interactions (7))*, phenytoin, and tolbutamide have been studied *in vivo* 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 or 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 *1/*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 0.5% to 1.0% in various ethnic groups *(see Dosage and Administration (2.7), Use in Specific Populations (8.8))*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Celecoxib was not carcinogenic in Sprague-Dawley rats after oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-times the human exposure as measured by the AUC_{0-24} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg twice daily) for two years.

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

Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC_{0-24}). At ≥ 50 mg/kg/day (approximately 6-times human exposure based on the AUC_{0-24} at 200 mg twice daily) there was increased preimplantation loss.

13.2 Animal Toxicology

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients with hyperosmia as well as minimal to slight dilation of the semicircular canals 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 effect 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 Osteoarthritis

Celecoxib capsules have demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib capsules were evaluated for treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with celecoxib capsules 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib capsules at doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 12 to 48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of celecoxib capsules was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

14.2 Rheumatoid Arthritis

Celecoxib capsules has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib capsules were evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. In patients with OA, treatment with celecoxib capsules 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib capsules at doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 12 to 48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of celecoxib capsules was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

Although celecoxib capsules 100 mg twice daily and 200 mg twice daily provided similar overall effectiveness, some patients derived additional benefit from the 200 mg twice daily doses. Doses of 400 mg twice daily provided no additional benefit above that seen with 100 mg to 200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis (NCT00652925)

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 years to 17 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with currently inactive systemic features), received one of the following treatments: celecoxib 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The response rates were based upon the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) criterion which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates at week 12 were 69%, 80% and 67% in the celecoxib 3 mg/kg twice daily, celecoxib 6 mg/kg twice daily, and naproxen 7.5 mg/kg twice daily respectively.

The efficacy and safety of celecoxib capsules for JRA have not been studied beyond six months. The long-term cardiovascular toxicity in children exposed to celecoxib capsules has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to celecoxib capsules or other COX-2 selective and non-selective NSAIDs *(see Boxed Warning, Warnings and Precautions (5.5), and Clinical Studies (14.3))*.

14.4 Analgesic Spondylitis

Celecoxib capsules was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. Celecoxib capsules at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), functional disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index).

In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg celecoxib capsule doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to celecoxib capsules 400 mg, 53% than the placebo group, 44%, using the Ankylosing Spondylitis Response Criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 mm to 100 mm scale, in at least three of the four following domains: patient global pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

14.5 Analgesia, including Primary Dysmenorrhea

In acute analgesic studies of post-oral surgical pain, post-orthopedic surgical pain, and primary dysmenorrhea, celecoxib capsules relieved pain that was rated by patients as moderate to severe. Single doses *(see Dosage and Administration (2.6))* of celecoxib capsules provided pain relief within 60 minutes.

14.6 Cardiovascular Outcomes Trial: Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION; NCT00543216)

Design

The PRECISION trial was a double-blind randomized controlled trial of cardiovascular safety in OA and RA patients with or at high risk for cardiovascular disease comparing celecoxib with naproxen and ibuprofen. Patients were randomized to a starting dose of 100 mg twice daily of celecoxib, 600 mg three times daily of ibuprofen, or 375 mg twice daily of naproxen, with the option of escalating the dose as needed for pain management. Based on labeled doses, OA patients randomized to celecoxib capsules provided pain relief within 60 minutes.

The primary endpoint, the Antipainlet Trialists' Collaboration (APTC) composite, was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20 mg to 40 mg) for gastroprotection. Non-inferiority was prespecified as a hazard ratio (HR) of ≤ 1.12 in both ITT and mITT analyses, and the upper 95% CI of ≤ 1.33 for ITT analysis and ≤ 1.40 for mITT analysis.

The primary analysis results for ITT and mITT are described in Table 5.

Table 5. Primary Analysis of the Adjudicated APTC Composite Endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib	Ibuprofen	Naproxen
N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)
Pairwise Comparison	Celecoxib vs. Naproxen	Celecoxib vs. Ibuprofen	Ibuprofen vs. Naproxen
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)			
	Celecoxib	Ibuprofen	Naproxen
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	Celecoxib vs. Naproxen	Celecoxib vs. Ibuprofen	Ibuprofen vs. Naproxen
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.89, 1.40)

Table 6. Summary of the Adjudicated APTC Components*

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib	Ibuprofen	Naproxen
N	8,072	8,040	7,969
CV Death	68 (0.8%)	80 (1.0%)	86 (1.1%)
Non-Fatal MI	76 (0.9%)	92 (1.1%)	66 (0.8%)
Non-Fatal Stroke	51 (0.6%)	53 (0.7%)	57 (0.7%)
Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)			
	8,030	7,990	7,933
CV Death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Non-Fatal MI	58 (0.7%)	76 (1.0%)	53 (0.7%)
Non-Fatal Stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)

*A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

In the ITT analysis population through 30 months, all-cause mortality was 1.6% in the celecoxib group, 1.8% in the ibuprofen group, and 2.0% in the naproxen group.

Ambulatory Blood Pressure Monitoring (ABPM) Substudy

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients at Month 4, celecoxib dosed at 100 mg twice daily decreased mean 24-hour systolic blood pressure (SBP) by 0.3 mmHg, whereas ibuprofen and naproxen at the doses taken increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of 3.9 mmHg (p=0.009) between celecoxib and naproxen.

14.7 Special Studies

Adenomatous Polyposis Prevention Studies (NCT00050594 and NCT00141193)

Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with celecoxib capsules: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated).

• In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 to 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 to 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.

• In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 to 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.

Celecoxib Long-Term Arthritis Safety Study (CLASS)

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients with OA and RA patients. Patients received celecoxib capsules 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for celecoxib capsules (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation, or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: celecoxib capsules, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between celecoxib capsules and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on celecoxib capsules and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3,105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively *(see Warnings and Precautions (5.4))*.

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with celecoxib capsules 400 mg twice daily are described in Table 7. Table 7 also displays results for patients less than or greater than 65 years of age. The difference in rates between celecoxib capsules alone and celecoxib capsules with ASA groups may be due to the higher risk for GI events in ASA users.

Table 7. Complicated and Symptomatic Ulcer Rates in Patients Taking Celecoxib Capsules 400 mg Twice Daily (Kaplan-Meier Rates at 9 months (%) Based on Risk Factors)

All Patients	
Celecoxib Capsules alone (n=3,105)	0.78
Celecoxib Capsules with ASA (n=882)	2.19
Patients <65 Years	
Celecoxib Capsules alone (n=2,025)	0.47
Celecoxib Capsules with ASA (n=403)	1.26
Patients ≥ 65 Years	
Celecoxib Capsules alone (n=1,080)	1.40
Celecoxib capsules with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking celecoxib capsules alone or celecoxib capsules with ASA were, respectively, 2.56% (n=243) and 6.85% (n=61) at 48 weeks. These results indicate that patients should be expected in patients with a prior history of ulcer disease *(see Warnings and Precautions (5.2) and Adverse Reactions (6.1))*.

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no difference between the celecoxib capsules, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for celecoxib capsules, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates at nine months for patients on low-dose ASA users at nine months in each of the three treatment groups were 1.1%, 1.4%, and 1.1%, respectively. There were no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to