## Indications and dosing

- **CELEBREX** should be used at the lowest effective dose for the shortest duration consistent with treatment goals for the individual patient.
- **CELEBREX** can be administered without regard to timing of meals.
- **CELEBREX** is available in 4 dosage forms and strengths: 50 mg, 100 mg, 200 mg, and 400 mg capsules.

### Osteoarthritis: **CELEBREX** is indicated for the management of the signs and symptoms of OA.

- **Starting dose:** 200 mg once daily or 100 mg twice per day.

### Rheumatoid arthritis: **CELEBREX** is indicated for the management of the signs and symptoms of RA.

- **Starting dose:** 100 mg to 200 mg twice per day.

### Acute pain in adults: **CELEBREX** is indicated for the management of acute pain in adults.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Start</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg initial dose</td>
<td>200 mg if needed</td>
</tr>
<tr>
<td>Days &gt;1</td>
<td>200 mg twice per day as needed</td>
<td></td>
</tr>
</tbody>
</table>

### Ankylosing spondylitis: **CELEBREX** is indicated for the management of signs and symptoms of ankylosing spondylitis.

- **Starting dose:** Single dose 200 mg (once per day) or divided (twice per day) doses.
- **If no effect after 6 weeks:** A trial of 400 mg daily may be worthwhile.
- **If no effect after 6 weeks on 400 mg daily:** A response is not likely and an alternate treatment should be considered.

### Primary dysmenorrhea: **CELEBREX** is indicated for the management of primary dysmenorrhea.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Start</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg initial dose</td>
<td>200 mg if needed</td>
</tr>
<tr>
<td>Days &gt;1</td>
<td>200 mg twice per day as needed</td>
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</tr>
</tbody>
</table>

### Juvenile rheumatoid arthritis (JRA): **CELEBREX** is indicated for the management of the signs and symptoms of JRA in pediatric patients ≥2 years.

<table>
<thead>
<tr>
<th>Patients 10 kg to 25 kg/22 lb to 55 lb</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>50 mg twice per day</td>
</tr>
<tr>
<td>Patients &gt;25 kg/&gt;55 lb</td>
<td>100 mg twice per day</td>
</tr>
</tbody>
</table>

### Special Populations: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B).

Initiate treatment with half of lowest recommended dose in adult patients who are known to be poor CYP2C9 metabolizers.

In patients with JRA who are known to be poor CYP2C9 metabolizers consider using alternative treatment.

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## Important Safety 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.
- **CELEBREX** is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

### 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.

Use **CELEBREX** at the lowest dose for the shortest duration possible to minimize risk of CV, GI and hepatic adverse events.

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

### Warnings and Precautions

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

**Hepatotoxicity:** Elevations of ALT or AST have been reported in patients with NSAIDs. In addition, rare, sometimes fatal cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. 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.

**Hypertension:** NSAIDs, including **CELEBREX**, 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 some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Please see additional Important Safety Information and Indications on next page and accompanying full Prescribing Information, including BOXED WARNING and Medication Guide.
Important Safety Information (continued)

Heart Failure and Edema: Avoid the use of CELEBREX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If CELEBREX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury and may cause a dose-dependent reduction in prostaglandin formation, which may precipitate overt renal decompensation. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of CELEBREX in patients with advanced renal disease unless benefits are expected to outweigh the risk of worsening renal function. If CELEBREX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

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. CELEBREX is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Exacerbation of Asthma Related to Aspirin Sensitivity: CELEBREX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity).

Serious Skin Reactions: Serious skin reactions have occurred following treatment with CELEBREX, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal. Discontinue CELEBREX at first appearance of skin rash or other signs of hypersensitivity.

Premature Closure of Fetal Ductus Arteriosus: Celecoxib may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

Hematologic Toxicity: Anemia has occurred in NSAID treatment patients. Monitor hemoglobin or hematocrit in patients with signs or symptoms of anemia. NSAIDs, including CELEBREX, may increase the risk of bleeding events. Monitor patients for signs of bleeding.

Disseminated Intravascular Coagulation (DIC): Because of the risk of disseminated intravascular coagulation with use of CELEBREX in pediatric patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, and inform patients and their caregivers to report symptoms as soon as possible.

Drug Interactions

Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking CELEBREX with drugs that interfere with hemostasis. Concomitant use of CELEBREX and analgesic dose of aspirin is not generally recommended.

ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with CELEBREX may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

ACE Inhibitors and ARBs: Concomitant use with CELEBREX in the 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.

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects.

Digoxin: Concomitant use with CELEBREX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.

Adverse Reactions: The 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.

Use in Specific Populations

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

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of CELEBREX in women who have difficulties conceiving.

Indications

CELEBREX is indicated for the management of the signs and symptoms of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years and older, and ankylosing spondylitis; for the management of acute pain in adults, and for the management of primary dysmenorrhea.

Please see accompanying full Prescribing Information, including BOXED WARNING and Medication Guide.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CELEBREX safely and effectively. See full prescribing information for CELEBREX.

CELEBREX® (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)

- CELEBREX 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)

5.2 Pathological Fractures and osteoporosis

5.3 Hepatotoxicity

5.4 Hypertension

5.5 Heart Failure and Edema

5.6 Renal Toxicity and Hyperkalemia

5.7 Anaphylactic Reactions

7. DRUG INTERACTIONS

- Drugs that Interfere with Hemeostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking CELEBREX with drugs that interfere with hemeostasis. Concomitant use of CELEBREX and analgesic doses of aspirin is not generally recommended (7)

- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with CELEBREX may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

- ACE inhibitors and ARBs: Concomitant use with CELEBREX 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 CELEBREX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14. CLINICAL STUDIES

14.1 Osteoarthritis

14.2 Rheumatoid Arthritis

14.3 Juvenile Rheumatoid Arthritis

14.4 Ankylosing Spondylitis

14.5 Analgesia, Including Primary Dysmenorrhea

14.6 Special Studies

16. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
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)]
- **Celebrex** is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. [See Contraindications (4) and Warnings and Precautions (5.1)]

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

### 1. INDICATIONS AND USAGE

**Celebrex** is 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

**General Dosing Instructions**
Carefully consider the potential benefits and risks of **Celebrex** and other treatment options before deciding to use **Celebrex**. 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.

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

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

**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.

**Ankylosing Spondylitis**
For AS, the dosage of **Celebrex** 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.

**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.

**Special Populations**

**Hepatic Impairment**
In patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of **Celebrex** in patients with severe hepatic impairment is not recommended [See Warnings and Precautions (5.5), 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 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

**Celebrex** (celecoxib) capsules:
- 50 mg white, with reverse printed white on red band and cap with markings of 7767 on the cap and 50 on the body.
- 100 mg white, with reverse printed white on blue band and cap with markings of 7767 on the cap and 100 on the body.
- 200 mg white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body.
- 400 mg white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body.

### 4. CONTRAINDICATIONS

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

### 5. WARNINGS AND PRECAUTIONS

#### 5.1 Cardiovascular Thrombotic Events

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

In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for **Celebrex** 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with **Celebrex** 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/665 subjects), respectively, compared to 0.9% (8/879 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 [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 10-14 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 **Celebrex** in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If **Celebrex** is 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 **Celebrex**. 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 3-6 months, and in about 2%-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, aspirin, anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and pregnancy. The risk of major gastrointestinal events in elderly and debilitated patients is increased compared to younger 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 (14.6)].

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 active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue Celecoxib until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal (ULN)) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminating 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, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for Celecoxib and 5% for placebo, and approximately 0.2% of patients taking Celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

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, etc.), discontinue Celecoxib immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including Celecoxib 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)].

The rates of hypertension from the CLASS trial in the Celecoxib, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [see Clinical Studies (14.6)].

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 (14.6)], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on Celecoxib 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 4.3%, 6.9% and 4.7%, respectively.

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

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

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

No information is available from controlled clinical studies regarding the use of Celecoxib in patients with 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. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Celecoxib [see Drug Interactions (7)]. Avoid the use of Celecoxib in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Celecoxib is 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-hyperaldosteronism 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 subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps, severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity is seen between aspirin and other NSAIDs, discontinue Celecoxib and other NSAIDs in patients with a history of aspirin-sensitive asthma (see Contraindications (4)). When Celecoxib is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

Serious skin reactions have occurred following treatment with Celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of Celecoxib at the first appearance of skin rash or any other sign of hypersensitivity. Celecoxib is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus

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

5.11 Hematological Toxicity

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

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

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

5.12 Masking of Inflammation and Fever

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

5.13 Laboratory Monitoring

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

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving Celecoxib compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.
Among the most common reasons for discontinuation due to adverse events in the Controlled Arthritis Trials in 0.8% and 0.7% of IBU = Ibuprofen 800 mg three times daily.

0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

Table 1: Adverse Events Occurring in >2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Pre-marketing Controlled Arthritis Trials
Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

The following adverse reactions occurred in 0.1 - 1.9% of patients treated with CELEBREX (100 - 200 mg twice daily or 200 mg once daily):

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting

Cardiovascular: Hypersensitivity, angina pectoris, coronary artery disorder, myocardial infarction

General: Leg cramps, hypotonia, hyposthesia, migraine, paresthesia, vertigo

Hematologic Toxicity [Warnings and Precautions (5.11)]

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients:

Hematologic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, cough, dyspnea, laryngitis, pneumonia

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

Application site disorders: Cellulitis, dermatitis contact

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

Renal: Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study [see Special Studies (14.6)]
Hematological Events: The incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients on CELEBREX 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 (1.9%). The lower incidence of events with CELEBREX was maintained with or without aspirin use [see Clinical Pharmacology (12.2)].

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29% and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

Juvenile Rheumatoid Arthritis Study
In a 12-week, double-blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg twice daily, 82 patients were treated with celecoxib 6 mg/kg twice daily, and 83 patients were treated with naproxen 7.5 mg/kg twice daily. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness (Table 2). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice daily had no observable deleterious 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 exacerbations of uveitis or systemic features of JRA among treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg twice daily. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected 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)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Doses Twice Daily</th>
<th>Celecoxib</th>
<th>Celecoxib</th>
<th>Celecoxib</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 mg/kg</td>
<td>6 mg/kg</td>
<td>7.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Any Event</td>
<td>64 70 72</td>
<td>77 92 83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>5 5 5</td>
<td>5 6 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26 24 36</td>
<td>25 16 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain NOS</td>
<td>4 7 7</td>
<td>7 9 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8 6 10</td>
<td>9 7 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>3 6 11</td>
<td>3 6 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.8% 5.3%</td>
<td>6.8% 5.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.8% 1.6%</td>
<td>2.8% 1.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.1% 0.8%</td>
<td>2.1% 0.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.5% 9.8%</td>
<td>12.5% 9.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>13 11 18</td>
<td>13 11 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 9 11</td>
<td>8 9 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>25 20 27</td>
<td>25 20 27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 6 5</td>
<td>5 6 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury and Poisoning</td>
<td>4 6 5</td>
<td>4 6 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations*</td>
<td>3 11 7</td>
<td>3 11 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8 10 17</td>
<td>8 10 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 7 4</td>
<td>3 7 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td>17 11 21</td>
<td>17 11 21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache NOS</td>
<td>13 10 16</td>
<td>13 10 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness (excl vertigo)</td>
<td>1 1 1</td>
<td>1 1 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>8 15 15</td>
<td>8 15 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10 7 18</td>
<td>10 7 18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

Other Pre-Approval Studies

Adverse Events from Ankylosing Spondylitis Studies: A total of 378 patients were treated with Celebrex in placebo- and active-controlled AS studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the AS studies were similar to those reported in the OA/RA studies.

Adverse Events from Analgesia and Dysmenorrhea Studies: Approximately 1,700 patients were treated with Celebrex in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of Celebrex were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

The APC and PreSAP Trials

Adverse reactions from long-term, placebo-controlled polyp prevention studies: Exposure to Celebrex in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years [see Special Studies Adenomatous Polyp Prevention Studies (14.6)]. Some adverse reactions occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks; see Adverse events from Celebrex pre-marketing controlled arthritis trials, above). The adverse reactions for which these differences in patients treated with Celebrex were greater as compared to the arthritis pre-marketing trials were as follows:

<table>
<thead>
<tr>
<th>Celebrex</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 to 800 mg daily</td>
<td>N=2285</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5% 7.0%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>4.7% 3.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8% 5.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.2% 2.1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.8% 1.6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.5% 9.8%</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>2.1% 0.8%</td>
</tr>
</tbody>
</table>

The following additional adverse reactions occurred in ≥1% and <1% of patients taking Celebrex, at an incidence greater than placebo in the long-term polyp prevention studies, 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

7. DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with celecoxib.

Table 3: Clinically Significant Drug Interactions with Celecoxib

<table>
<thead>
<tr>
<th>Drugs That Interact with Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib and antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.11)].</td>
</tr>
</tbody>
</table>

Clinical Impact:

- Monitor patients with concomitant use of Celebrex with antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.11)].

Aspirin

Clinical Impact:

- Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)].

- In two studies in healthy volunteers, and in patients with osteoarthritis and established heart disease respectively, celecoxib (200–400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100–325 mg).

Intervention:

- Monitor patients with concomitant use of Celebrex with antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.11)].

ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers

Clinical Impact:

- NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (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:

- Monitor blood pressure to ensure that the desired blood pressure is obtained.

- When these drugs are administered concomitantly, patients should be adequately hydrated. Monitor blood pressure function at the beginning of the concomitant treatment and periodically thereafter.
**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 and digoxin, monitor serum digoxin levels.

**Digoxin**

**CYP2D6 substrates**

**Clinical Impact:** In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6 (e.g. atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.

**Intervention:** Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates. [see Clinical Pharmacology (12.3)].

**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 and lithium, monitor patients for signs of lithium toxicity.

**Corticosteroids**

**Clinical Impact:** Concomitant use of corticosteroids with Celecoxib may increase the risk of GI ulceration or bleeding.

**Intervention:** Monitor patients with concomitant use of Celecoxib with corticosteroids for signs of bleeding [see Warnings and Precautions (5.2)].

8. **USE IN SPECIFIC POPULATIONS**

8.1 **Pregnancy**

**Pregnancy Category C.** Pregnancy category D from 30 weeks of gestation onward.

**Risk Summary**

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

There are no adequate and well-controlled studies of Celecoxib in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. 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 of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternabne fused and sternabne misshapen) 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, prostanoids 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.

**Clinical Considerations**

**Labor or Delivery**

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

**Data**

**Human Data**

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

**Animal data**

Celecoxib at oral doses ≥150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC0-24) caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternaabne fused and sternaabne misshapen after 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 AUC0-24 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 AUC0-24 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 rats (approximately 7-fold human exposure as measured by the AUC0-24 at 200 mg twice daily). The effects of Celecoxib on labor and delivery in pregnant women are unknown.

8.2 **Lactation**

**Risk Summary**

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of Celecoxib in breast milk. The calculated average daily infant dose was 10-40 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 is 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.
8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including CELEBREX, may delay or prevent rupture of ovarian follicles, which has been associated with anovulation and 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 CELEBREX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

CELEBREX is 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 CELEBREX has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [see Boxed Warning, Warnings and Precautions (5.12), 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 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 (5.12), Adverse Reactions (6.3), 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)].

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, 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, 5.13)].

Of the total number of patients who received CELEBREX in pre-approval clinical trials, more than 3,300 were 65–74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients [see Warnings and Precautions (5.4, 5.6)].

8.6 Hepatic Impairment

The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)].

8.7 Renal Impairment

CELEBREX is not recommended in patients with severe renal insufficiency [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer CELEBREX 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 (2.6) and Clinical Pharmacology (12.5)].

10. OVERDOSAGE

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

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 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 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (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 overdose treatment contact a poison control center (1-800-222-1222).

11. DESCRIPTION

CELEBREX (celecoxib) capsule 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] benzene sulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C₂₇H₁₈F₃N₂O₄S, and it has the following chemical structure:

![Chemical Structure of Celecoxib](image)

CELEBREX is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH ranges.

The inactive ingredients in CELEBREX include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povodine and sodium lauryl sulfate.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CELECOXB has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

Celecoxib is a potent inhibitor of prostaglandin synthesis in vitro. Celecoxib concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

Platelets

In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of CELEBREX.

Fluid Retention

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

12.3 Pharmacokinetics

Celecoxib exhibits dose-proportional increase in exposure after oral administration up to 200 mg twice daily and less than proportional increase at higher doses. It has extensive distribution and high protein binding. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

Absorption

Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose-proportional up to 200 mg twice daily; at higher doses there are less than proportional increases in Cmax and AUC [see Food Effects]. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 4.

### Table 4: Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects

<table>
<thead>
<tr>
<th>Mean (%)CV PK Parameter Values</th>
<th>Cmax, ng/mL</th>
<th>Tmax, hr</th>
<th>Effective t1/2, hr</th>
<th>Vd/F, L</th>
<th>CL/F, L/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>705 (38)</td>
<td>2.8 (37)</td>
<td>11.2 (31)</td>
<td>429 (34)</td>
<td>27.7 (28)</td>
<td></td>
</tr>
</tbody>
</table>

1 Subjects under fasting conditions (n=36, 19-52 yrs.)
Food Effects

When CelaBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

Coadministration of CelaBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. CelaBREX, at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in Cmax, Tmax or t1/2 after administration of capsule contents on applesauce [see Dosage and Administration (2)].

Distribution

In healthy subjects, celecoxib is highly protein bound (<97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin, and to a lesser extent, α1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Metabolism

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

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process, thus making terminal half-life and first-pass determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Specific Populations

Geriatric

At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose [see Dosage and Administration (2.7) and Use in Specific Populations (8.5)].

Pediatric

The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient. Twice-daily administration of 50 mg capsules to JRA patients weighing ≥12 to <25 kg and 100 mg capsules to JRA patients weighing ≥25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (see Dosage and Administration (2.4)). Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks. Race

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

Hepatic Impairment

A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CelaBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of CelaBREX in patients with severe hepatic impairment is not recommended [see Dosage and Administration (2.6) and Use in Specific Populations (8.6)].

Renal Impairment

In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CelaBREX is 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.

In vivo studies have shown the following:

Aspirin

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 CelaBREX 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 twofold 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)], phenytion, 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 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*2 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.8)].

13. NONCLINICAL TOXICLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Celecoxib was not carcinogenic in Sprague-Dawley rats given 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 AUC0-24 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 AUC0-24 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 AUC0-24). At ≤50 mg/kg/day (approximately 6-times human exposure based on the AUC0-24 at 200 mg twice daily) there was increased preimplantation loss.

13.2 Animal Toxicology

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

14. CLINICAL STUDIES

14.1 Osteoarthritis

CelaBREX has demonstrated significant reduction in joint pain compared to placebo. CelaBREX was 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 CelaBREX 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 these 12-week studies of pain accompanying OA flare, CelaBREX doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of CelaBREX 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

Celebrex has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celebrex was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. Celebrex was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. Celebrex doses of 100 mg twice daily and 200 mg twice daily were similar in effectiveness and both were comparable to naproxen 500 mg twice daily. Although Celebrex 100 mg twice daily and 200 mg twice daily provided similar overall effectiveness, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100-200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis

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); celecoxib 6 mg/kg (to a maximum of 300 mg); 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 treatment groups, respectively.

The efficacy and safety of Celebrex for JRA have not been studied beyond six months. The long-term cardiovascular toxicity in children exposed to Celebrex has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to Celebrex or other COX-2 selective and non-selective NSAIDs (see Boxed Warning, Warnings and Precautions (5.12)).

14.4 Ankylosing Spondylitis

Celebrex was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. Celebrex at doses of 100 mg twice daily, 200 mg once daily or 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), global 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 Celebrex doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to Celebrex 400 mg, 53% than to placebo, 44%, using the Assessment in Ankylosing Spondylitis (ASAS) 20 criterion, which is a composite of clinical, laboratory, and functional measures of JRA. 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 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 models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, Celebrex relieved pain that was rated by patients as moderate to severe. Single doses (see Dosage and Administration (2.6)) of Celebrex provided pain relief within 60 minutes.

14.6 Special Studies

Adenomatous Polyp Prevention Studies

Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with Celebrex: 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 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 PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 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)

This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received Celebrex 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 Celebrex (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: Celebrex, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between Celebrex and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on Celebrex and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3105). 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 Celebrex 400 mg twice daily are described in Table 4. Table 4 also displays results for patients less than or greater than 65 years of age. The difference in rates between Celebrex alone and Celebrex with ASA groups may be due to the higher risk for GI events in ASA users.

Table 5: Complicated and Symptomatic Ulcer Rates in Patients Taking Celebrex 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Celebrex alone (n=3105)</th>
<th>Celebrex with ASA (n=882)</th>
<th>Patients &lt;65 Years</th>
<th>Celebrex alone (n=2025)</th>
<th>Celebrex with ASA (n=403)</th>
<th>Patients &gt;65 Years</th>
<th>Celebrex alone (n=1080)</th>
<th>Celebrex with ASA (n=479)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.78</td>
<td>2.19</td>
<td>Celebrex alone</td>
<td>0.47</td>
<td>1.26</td>
<td>Celebrex alone</td>
<td>1.40</td>
<td>3.06</td>
</tr>
</tbody>
</table>

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking Celebrex alone or Celebrex with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see Warnings and Precautions (5.4) and Adverse Reactions (6.1)).

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thrombembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the Celebrex, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for Celebrex, 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 for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was 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 a similar degree.

Endoscopic Studies

The correlation between findings of short-term endoscopic studies with Celebrex and the relative incidence of clinically significant serious upper GI events with long-term use has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving Celebrex in controlled and open-label trials (see Warnings and Precautions (5.4) and Clinical Studies (14.6)).

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking Celebrex 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, Celebrex was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial (see Clinical Studies (14.6)).

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled trials in 2157 OA patients. At endoscopy, baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of Celebrex (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all doses of Celebrex the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with Celebrex and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (≤325 mg/day). In the Celebrex groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.
16. HOW SUPPLIED/STORAGE AND HANDLING

CELEBREX (celecoxib) 50 mg capsules are white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1515-01</td>
<td>bottle of 60</td>
</tr>
</tbody>
</table>

CELEBREX (celecoxib) 100 mg capsules are white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

<table>
<thead>
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<th>Size</th>
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<tbody>
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<td>bottle of 100</td>
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<tr>
<td>0025-1520-51</td>
<td>bottle of 500</td>
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<tr>
<td>0025-1520-34</td>
<td>carton of 100 unit dose</td>
</tr>
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</table>

CELEBREX (celecoxib) 200 mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

<table>
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<th>Size</th>
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<tbody>
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<td>0025-1525-31</td>
<td>bottle of 100</td>
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<tr>
<td>0025-1525-51</td>
<td>bottle of 500</td>
</tr>
<tr>
<td>0025-1525-34</td>
<td>carton of 100 unit dose</td>
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</table>

CELEBREX (celecoxib) 400 mg capsules are white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body, supplied as:

<table>
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<tr>
<th>NDC Number</th>
<th>Size</th>
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<tbody>
<tr>
<td>0025-1530-02</td>
<td>bottle of 60</td>
</tr>
<tr>
<td>0025-1530-01</td>
<td>carton of 100 unit dose</td>
</tr>
</tbody>
</table>

Storage

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

17. PATIENT COUNSELING INFORMATION

Advertise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

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

Gastrointestinal Bleeding, Ulceration, and Perforation

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

Hepatotoxicity

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

Heart Failure and Edema

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

Anaphylactic Reactions

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

Serious Skin Reactions

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

Female Fertility

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

Fetal Toxicity

Inform pregnant women to avoid use of CELEBREX and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)].

Avoid Concomitant Use of NSAIDs

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

Use of NSAIDs and Low-Dose Aspirin

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

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Issued: May 2016
NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

Who should not take NSAIDs?

Do not take NSAIDs:
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy.
- You should not take NSAIDs after 29 weeks of pregnancy
- are breastfeeding or plan to breast feed.

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

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

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

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

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

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

The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs” or “SNRIs”
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol

NSAIDs should only be used:
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

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

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions

Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

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

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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