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.

- **200 mg once daily or 100 mg twice daily**

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

- **100 mg to 200 mg twice daily**

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

| Day 1 | 400 mg initial dose + 200 mg if needed |
| Days >1 | 200 mg twice per day as needed |

**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.

| Day 1 | 400 mg initial dose + 200 mg if needed |
| Days >1 | 200 mg twice per day as needed |

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

- **Patients 10 kg to 25 kg / 22 lb to 55 lb:** 50 mg twice per day
- **Patients >25 kg / >55 lb:** 100 mg twice per day

**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 and Indications

**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 and Indications (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 (third trimester).

Hematologic Toxicity: Anemia has occurred in NSAID treatment patients. Monitor hemoglobin or hematocrit in patients with any 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 oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs), is not 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.

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.

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.

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.
CELEBREX® (celecoxib) capsules, for oral use

Initial U.S. Approval: 1998

WARNINGS AND PRECAUTIONS

• Hepatotoxicity: inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
• Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
• Heart Failure and Edema: Avoid use of CELEBREX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
• Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of CELEBREX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
• Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
• Exacerbation of Asthma Related to Aspirin Sensitivity: CELEBREX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
• Serious Skin Reactions: Discontinue CELEBREX at first appearance of skin rash or other signs of hypersensitivity (5.9)
• Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
• Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

• Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular and 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)

ADVERSE REACTIONS

Most common adverse reactions in arthritis trials (≥2% and >placebo) are: abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

• Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]): Monitor patients for bleeding who are concomitantly taking CELEBREX with drugs that interfere with hemostasis. Concomitant use of CELEBREX and analgesic doses of aspirin is not generally recommended (7)
• Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with 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)
• Dipoxin: Concomitant use with CELEBREX can increase serum concentration and prolong half-life of dipoxin. Monitor serum dipoxin levels (7)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
• Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of CELEBREX in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2019
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1.2 Rheumatoid Arthritis
1.3 Juvenile Rheumatoid Arthritis
1.4 Ankylosing Spondylitis
1.5 Acute Pain
1.6 Primary Dysmenorrhea
2. DOSAGE AND ADMINISTRATION
2.1 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.

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
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3. **DOSE FORMS AND STRENGTHS**

**CELEBREX** (celecoxib) capsules:
- 50 mg white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body.
- 100 mg white, with reverse printed white on blue band of body 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, 5.9)].
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients [see Warnings and Precautions (5.7, 5.8)].
- In the setting of CAGB surgery [see Warnings and Precautions (5.1)].
- In patients who have demonstrated allergic-type reactions to sulfaanilides.

5. **WARNINGS AND PRECAUTIONS**

5.1 **Cardiovascular Thrombotic Events**

Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar 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 week of treatment. The increase in CV thrombotic risk has been observed consistently at higher doses.

In the APC (Adenoma Prevention with Celecoxib) trial, there was about a threefold increased risk of the composite endpoint of cardiovascular death, MI, or stroke for the CELEBREX 400 mg twice daily and CELEBREX 200 mg twice daily treatment arms compared to placebo. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [see Clinical Studies (14.7)].

A randomized controlled trial entitled the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) was conducted to assess the relative cardiovascular thrombotic risk of a COX-2 inhibitor, celecoxib, compared to the non-selective NSAIDs naproxen and ibuprofen. Celecoxib 100 mg twice daily was non-inferior to naproxen 375 to 500 mg twice daily and ibuprofen 600 to 800 mg three times daily for the composite endpoint of the Antiplatelet Trialists’ Collaboration (APTC), which consists of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke [see Clinical Studies (14.6)].

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

**Status Post Coronary Artery Bypass Graft (CABG) Surgery**

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

**Post-MI Patients**

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 1000 person-years in NSAID-treated patients compared to 12 per 1000 person-years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative rate 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 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

**Risk Factors for GI Bleeding, Ulceration, and Perforation**

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients with no such risk factors. Older patients (65 years of age and older) have been shown to be at greater risk for serious GI adverse events. NSAIDs including celecoxib occurred in approximately 1% of patients treated for long-term therapy.

In addition, 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 such risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

**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 CELEBREX 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)].
5.6 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 compensation. 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 CELEBREX in patients with advanced renal disease. The renal effects of CELEBREX may hasten the progression of renal dysfunction in patients with preexisting renal disease. Correct volume status in dehydrated or hypovolemic patients prior to initiating CELEBREX. Monitor renal function in patients with renal or hepatic impairment, heart failure, diabetes, or hypothyroidism during use of CELEBREX [see Drug Interactions (7)]. Avoid the use of CELEBREX in patients with advanced renal disease unless the 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.

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 hyponorenic-hypoaldosteronism state.

5.7 Anaphylactic Reactions
Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. 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 [see Contraindications (4) and Warnings and Precautions (5.8)]. Seek emergency help if any anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subgroup of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, CELEBREX is contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When CELEBREX 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 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. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CELEBREX at the first appearance of skin rash or any other sign of hypersensitivity. CELEBREX 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 CELEBREX, 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 CELEBREX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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

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

5.12 Masking of Inflammation and Fever
The pharmacological activity of CELEBREX 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 CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.14 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.

6. ADVERSE REACTIONS

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

- **Cardiovascular Thrombotic Events** [see Warnings and Precautions (5.1)]
- **GI Bleeding, Ulceration and Perforation** [see Warnings and Precautions (5.2)]
- **Hepatotoxicity** [see Warnings and Precautions (5.3)]
- **Hypertension** [see Warnings and Precautions (5.4)]
- **Heart Failure and Edema** [see Warnings and Precautions (5.5)]
- **Renal Toxicity and Hyperkalemia** [see Warnings and Precautions (5.6)]
- **Anaphylactic Reactions** [see Warnings and Precautions (5.7)]
- **Serious Skin Reactions** [see Warnings and Precautions (5.9)]
- **Hematologic Toxicity** [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Of the CELEBREX-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

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.

<table>
<thead>
<tr>
<th>Table 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials</th>
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<tbody>
<tr>
<td><strong>GI</strong></td>
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<tr>
<td>Abdominal Pain</td>
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<td>Diarrhea</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Flatulence</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Periostal Edema</td>
</tr>
<tr>
<td>Injury-Accidental</td>
</tr>
<tr>
<td><strong>Central, Peripheral Nervous system</strong></td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

CBX = CELEBREX 100 mg to 200 mg twice daily or 200 mg once daily; NAP = Naproxen 500 mg twice daily; DCF = Diclofenac 75 mg twice daily; IBU = Ibuprofen 800 mg three times daily.

In placebo- or active-controlled clinical trials, the discontinuation rate observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The following adverse reactions occurred in 0.1% to 1.9% of patients treated with CELEBREX (100 mg to 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:** Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

**General:** Hypersensitivity, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

**Central, peripheral nervous system:** Leg cramps, hypertonitia, hypoesthesia, migraine, paresthesia, vertigo

**Hearing and vestibular:** Deafness, tinnitus

**Heart rate and rhythm:** Palpitation, tachycardia

**Liver and biliary:** Hepatic enzyme increased (including SGOT increased, SGPT increased)

**Metabolic and nutritional:** Blood urea nitrogen (BUN) increased, creatine phosphokinase (CPK) increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

**Musculoskeletal:** Arthralgia, arthritis, myalgia, synovitis, tendinitis

**Platelets (bleeding or clotting):** ECChymosis, epistaxis, thrombocytopenia

**Psychiatric:** Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

**Hemic:** Anemia

**Respiratory:** Bronchitis, bronchospasm, bronchospasm aggravated, cough, dysnea, 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

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

**Cardiovascular:** Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis

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

**General:** Sepsis, sudden death

**Liver and biliary:** Cholelithiasis

**Hemic and lymphatic:** Thrombocytopenia

**Nervous:** Ataxia, suicide [see Drug Interactions (7.1)]

**Renal:** Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study [see Clinical Studies (14.7)]

**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).

**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.

**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 Ankylosing Spondylitis Studies:** Approximately 1,700 patients were treated with CELEBREX in analsis 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 analsis 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 mg to 800 mg daily for up to 3 years [see Special Studies Adenomatous PolyP Prevention Studies (14.7)]. 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 than compared to the arthritis pre-marketing trials were as follows:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Doses Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib 3 mg/kg N=77</td>
</tr>
<tr>
<td>Any Event</td>
<td>64 70 72</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>5 5 5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26 24 36</td>
</tr>
<tr>
<td>Abdominal pain NOS</td>
<td>4 7 7</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8 6 10</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>3 6 11</td>
</tr>
<tr>
<td>Diarrhea NOS</td>
<td>5 4 8</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 4 11</td>
</tr>
<tr>
<td>General</td>
<td>13 11 18</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 9 11</td>
</tr>
<tr>
<td>Infections</td>
<td>25 20 27</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 6 5</td>
</tr>
<tr>
<td>Injury and Poisoning</td>
<td>4 6 5</td>
</tr>
<tr>
<td>Investigations*</td>
<td>3 11 7</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8 10 17</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 7 4</td>
</tr>
<tr>
<td>Nervous System</td>
<td>17 11 21</td>
</tr>
<tr>
<td>Headache NOS</td>
<td>13 10 16</td>
</tr>
<tr>
<td>Dizziness (excl vertigo)</td>
<td>1 1 7</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8 15 15</td>
</tr>
<tr>
<td>Cough</td>
<td>7 7 8</td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10 7 18</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 urea nitrogen increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

The following additional adverse reactions occurred in ≥0.1% 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:

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>CELEBREX (400 to 800 mg daily) N=2285 Placebo N=1303</th>
</tr>
</thead>
<tbody>
<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 adverse reactions occurred in ≥0.1% 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:

- Anemia
- Albuminuria
- Anorexia
- Anxiety
- Appetite increased
- Depression
- Nervousness
- Urticaria
- Edema (dry socket) in the post-oral surgery pain studies.
### 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>Drug Category</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs and Salicylates</strong></td>
<td>Concomitant use of Celecoxib with other NSAIDs or salicylates may increase the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)].</td>
<td>During concomitant use of Celecoxib and other NSAIDs or salicylates, monitor patients for signs of worsening renal function.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Concomitant use of methotrexate and celecoxib may increase the risk for methotrexate toxicity [e.g., neutropenia, thrombocytopenia, renal dysfunction].</td>
<td>During concomitant use of Celecoxib and methotrexate, monitor patients for methotrexate toxicity.</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td>Concomitant use of Celecoxib and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).</td>
<td>During concomitant use of Celecoxib and pemetrexed in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before the day of, and two days following pemetrexed administration.</td>
</tr>
<tr>
<td><strong>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</strong></td>
<td>Concomitant use of ACE inhibitors, ARBs, or beta-blockers (including propranolol), in patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.</td>
<td>During concomitant use of Celecoxib and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of Celecoxib and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)]. When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.</td>
</tr>
<tr>
<td><strong>CYP2C9 Inhibitors or inducers</strong></td>
<td>Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g., fluconazole, indomethacin) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of celecoxib.</td>
<td>Evaluate each patient’s medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers. [see Clinical Pharmacology (12.3)].</td>
</tr>
</tbody>
</table>

#### Diuretics

Clinical Impact: Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.

Intervention: During concomitant use of CELEBREX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].

#### Digoxin

Clinical Impact: The concomitant use of Celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.

Intervention: During concomitant use of CELEBREX and digoxin, monitor serum digoxin levels.

#### Lithium

Clinical Impact: NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.

Intervention: During concomitant use of CELEBREX and lithium, monitor patients for signs of lithium toxicity.

#### Methotrexate

Clinical Impact: Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity [e.g., neutropenia, thrombocytopenia, renal dysfunction].

Intervention: During concomitant use of CELEBREX and methotrexate, monitor patients for methotrexate toxicity.

#### Cyclosporine

Clinical Impact: Concomitant use of CELEBREX and cyclosporine may increase cyclosporine’s nephrotoxicity.

Intervention: During concomitant use of CELEBREX and cyclosporine, monitor patients for signs of worsening renal function.

#### ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers

Clinical Impact:
- NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol).
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
- During concomitant use of CELEBREX and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
- During concomitant use of CELEBREX and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)].
- When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.

Intervention:
- Concomitant use of CELEBREX 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 mg to 400 mg daily) has demonstrated a lack of interference with the cardioselective antplatelet effect of aspirin (100 mg to 325 mg).
- During concomitant use of CELEBREX and pemetrexed, in the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed.
- In the absence of data regarding potential interaction between pemetrexed and NSAIDs with shorter half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before the day of, and two days following pemetrexed administration.
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 CELEBREX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

There are no adequate and well-controlled studies of CELEBREX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose (MRHD) of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternabrae fused and sternabrae 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, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss.

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

Clinical Considerations

Labor or Delivery

There are no studies on the effects of CELEBREX 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 Celebrex.

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, sternabrae fused and sternabrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6 times human exposure based on the 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 CELEBREX 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 CELEBREX in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when CELEBREX is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CELEBREX and any potential adverse effects on the breastfed infant from the CELEBREX 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 reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including 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 pauciarthritic, 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 articular features) are at increased risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). When NSAIDs including celecoxib are used in patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see Dosage and Administration (2.4), Warnings and Precautions (5.12), 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 (5.8) 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 (50 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, hemodiagnosis, 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) is a non-steroidal 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-pyrazole-1-yl)benzenesulfonamide and is a diaryl substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C₁₇H₁₄F₃N₃O₂S, and it has the following chemical structure:

![Chemical Structure of Celecoxib]

Celecoxib is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophilic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range. The inactive ingredients in CELEBREX include: crosscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Celecoxib has anaglogous, 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 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 red cell count, platelet count, or thrombocyte aggregation.

Fluid Retention

Inhibition of PGE2 synthesis may lead to sodium and water retention through decreased 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>
<thead>
<tr>
<th>Table 4</th>
<th>Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>705 (38)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.8 (37)</td>
</tr>
<tr>
<td>Effective t1/2 (hr)</td>
<td>11.2 (31)</td>
</tr>
<tr>
<td>Vss/F (L)</td>
<td>429 (34)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>27.7 (28)</td>
</tr>
</tbody>
</table>

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

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the 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 CELEBREX 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, 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 mg to 200 mg twice 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.

14.3 Juvenile Rheumatoid Arthritis (NCT00659295)

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 to 17 years of age with pauciarthritidal, polyarticular course JRA or systemic onset JRA (with currently active systemic features), received one of the following treatments: celecoxib 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The response rates were based upon the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The response rates at week 12 were 69%, 89%, 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 and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), 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 twice daily 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 50%, 53%, than to CELEBREX 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 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 surgical 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 Cardiovascular Outcomes Trial: Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION; NCT00346216)

Design

The PRECISION trial was a double-blind randomized controlled trial of cardiovascular safety in OA and RA patients with or at high risk for cardiovascular disease comparing celecoxib with naproxen and ibuprofen. Patients were randomized to a starting dose of 100 mg twice daily of celecoxib, 600 mg three times daily of ibuprofen, or 375 mg twice daily of naproxen, with the option of escalating the dose as needed for pain management. Based on labeled doses, OA patients randomized to celecoxib could not dose escalate.

The primary endpoint, the Antiplatelet Trialsist Collaboration (APT) composite, was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20-40 mg) for gastroprotection. Treatment randomization was stratified by baseline low-dose aspirin use.

Additionally, there was a 4-month substudy assessing the effects of the three drugs on blood pressure as measured by ambulatory monitoring.

Results

Among subjects with OA, only 0.2% (17/7259) escalated celecoxib to the 200 mg twice daily dose, whereas 54.7% (3956/7208) escalated ibuprofen to 800 mg three times daily, and 56.4% (432/791) escalated naproxen to the 500 mg twice daily dose. Among subjects with RA, 55.7% (453/815) escalated celecoxib to the 200 mg twice daily dose, 56.5% (470/832) escalated ibuprofen to 800 mg three times daily, and 54.6% (432/791) escalated naproxen to the 500 mg twice daily dose; however, the RA population accounted for only 10% of the trial population.

Because relatively few celecoxib patients overall (5.8% [470/8072]) dose-escalated to 200 mg twice daily, the results of the PRECISION trial are not suitable for determining the relative CV safety of celecoxib at 200 mg twice daily compared to ibuprofen and naproxen at the doses taken.
The primary endpoint of this outcome study was the incidence of complicated ulcers in the 3105 ASA users. The Kaplan-Meier rate for complicated ulcers 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 were daily are shown in Table 7. Table 7 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 7: 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>0.78</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELEBREX with ASA (n=882)</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td>Patients &lt;65 Years</td>
<td>CELEBREX alone (n=2025)</td>
<td>0.47</td>
</tr>
<tr>
<td>CELEBREX with ASA (n=403)</td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td>Patients ≥65 Years</td>
<td>CELEBREX alone (n=1080)</td>
<td>1.40</td>
</tr>
<tr>
<td>CELEBREX with ASA (n=479)</td>
<td>3.06</td>
<td></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 thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) were generally similar across CELEBREX, ibuprofen, and diclofenac 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. In the CLASS study, the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 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 (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 aspirin (≤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.

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients at Month 4, celecoxib dosed at 100 mg twice daily decreased mean 24-hour systolic blood pressure (SBP) by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of 3.9 mmHg (p=0.0009) between celecoxib and ibuprofen and a non-statistically significant difference of 1.8 (p=0.119) mmHg between celecoxib and naproxen.

#### Table 6: Summary of the Adjudicated APTC Components

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<thead>
<tr>
<th>Intent-To-Treat Analysis (ITT, through month 30)</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
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<tr>
<td>N</td>
<td>8,072</td>
<td>8,040</td>
<td>7,969</td>
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<tr>
<td>Subjects with Events</td>
<td>188 (2.3%)</td>
<td>218 (2.7%)</td>
<td>201 (2.5%)</td>
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<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib vs. Naproxen</td>
<td>0.93 (0.76, 1.13)</td>
<td>0.86 (0.70, 1.04)</td>
<td>1.08 (0.89, 1.31)</td>
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<td>HR (95% CI)</td>
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#### Table 7: Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

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### 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-labeled trials [see Warnings and Precautions (5.4) and Clinical Studies (14.7)].

#### 14.7 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 PRECISION-ABPM substudy, among the total of 444 analyzable patients at Month 4, celecoxib dosed at 100 mg twice daily decreased mean 24-hour systolic blood pressure (SBP) by 0.3 mmHg, whereas ibuprofen and naproxen at the doses taken increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of 3.9 mmHg (p=0.0009) between celecoxib and ibuprofen and a non-statistically significant difference of 1.8 (p=0.119) mmHg between celecoxib and naproxen.

**Table 5: Primary Analysis of the Adjudicated APTC Composite Endpoint**

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<thead>
<tr>
<th>Intent-To-Treat Analysis (ITT, through month 30)</th>
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<th>Ibuprofen</th>
<th>Naproxen</th>
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<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8,072</td>
<td>8,040</td>
<td>7,969</td>
</tr>
<tr>
<td>Subjects with Events</td>
<td>134 (1.7%)</td>
<td>155 (1.9%)</td>
<td>144 (1.8%)</td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib vs. Naproxen</td>
<td>0.90 (0.72, 1.14)</td>
<td>0.81 (0.64, 1.02)</td>
<td>1.12 (0.89, 1.40)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 (14.7)]. The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 OA and RA patients in whom 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>
<tr>
<th>NDC Number</th>
<th>Size</th>
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</thead>
<tbody>
<tr>
<td>0025-1520-31</td>
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</tr>
<tr>
<td>0025-1520-51</td>
<td>bottle of 500</td>
</tr>
<tr>
<td>0025-1520-34</td>
<td>carton of 100 unit dose</td>
</tr>
</tbody>
</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>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
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</thead>
<tbody>
<tr>
<td>0025-1525-31</td>
<td>bottle of 100</td>
</tr>
<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>
</tr>
</tbody>
</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>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<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]
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”, “antiplatelet drugs”, “anticoagulants”, “SSRIs” or “SNRIs”
- increasing doses of NSAIDs
- older age
- longer use of NSAIDs
- poor health
- smoking
- advanced liver disease
- drinking alcohol
- bleeding problems

**NSAIDs should only be used:**

- exactly as prescribed
- 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?**

**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 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
- 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 bone marrow or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swallowing 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.

This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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