Productive talks with your doctor are an important part of helping to manage your arthritis pain. Take the first step and use this guide to help prepare for your next doctor visit.* Complete the guide by filling in your answers right from your computer, or, if you prefer, print the guide and fill in your answers by hand.

By being honest about your symptoms and asking questions, you can help your doctor determine appropriate treatment options for you.

Your Arthritis Symptoms

Locate and select the areas where you feel arthritis pain:

- Ankle
- Elbow
- Shoulder
- Knee
- Other

Rate your arthritis pain:

- Extreme
- Severe
- Moderate
- Mild

*The information you enter in this Doctor Discussion Guide is for your own use only. Pfizer will not capture, collect, or retain any of the information you enter in this Discussion Guide.

Important Safety Information and Indications

All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam, increase the risk of heart attack or stroke that can lead to death. This may happen early in treatment and may increase with increasing doses of NSAIDs and with longer use of NSAIDs.

CELEBREX should never be used right before or after a heart surgery called “coronary artery bypass graft” (CABG).

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

NSAID medications, like CELEBREX, cause an increased risk of bleeding, ulcers, and tears (perforation) of the esophagus, stomach, and intestines, at any time during treatment, which can occur without warning and may cause death.

Please see continued BOXED WARNING and Important Safety Information on page 4 and accompanying full Prescribing Information including BOXED WARNING and Medication Guide.
Your Arthritis History

Are you experiencing arthritis pain for the first time?
- Yes
- No

If you’ve experienced arthritis pain before, is your current arthritis pain worse than it was 3 months ago?
- Yes
- No

Your Medications and Treatments

Select the medications you are currently taking. Be sure to add any that are not listed:
- Corticosteroids
- Type of blood-pressure medication
- Warfarin or similar blood-thinning agents
- Fluconazole
- Furosemide or thiazide diuretics
- Lithium
- Methotrexate
- Digoxin
- Aspirin
- CELEBREX® (celecoxib) capsules
- Other Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- SNRI or SSRI antidepressants
- Other (including vitamins and herbal supplements)

What are you currently doing to relieve your arthritis pain? (Select all that apply.)
- Taking pain relievers
- Using heat pads or ice packs
- Resting or not using the painful area
- Performing light activities or exercise
- Other

Please see Important Safety Information on pages 1 and 4 and accompanying full Prescribing Information including BOXED WARNING and Medication Guide.
Topics and Questions for Discussion

Select the topics that you'd like to discuss with your doctor to help him/her understand your arthritis pain:

- Local vs all-over pain
- Consistent vs intermittent pain
- Pain in the same place on both sides of the body
- Worst time of day for pain (ie, morning or night)
- Previous injuries
- Other

Tell your doctor if any of the following apply to you:

- A history of ulcers or bleeding in the stomach or intestines
- High blood pressure or heart failure
- Kidney or liver problems
- You are pregnant
- You are breastfeeding
- Allergies and type of reaction
- Your lifestyle/social history, including smoking, drinking alcohol, and exercise
- Other medical conditions or past medical history

Select the questions you'd like to ask your doctor:

- What could be the cause of my joint pain?
- With my medical history, which treatment is right for me?
- In addition to medicine, what other treatment options might help?
- I take low-dose aspirin. Which treatment is right for me?
- Other

Please see Important Safety Information on pages 1 and 4 and accompanying full Prescribing Information including BOXED WARNING and Medication Guide.
The next step is talking to your doctor.
Print this PDF and bring it to your appointment to help guide your discussion.

Important Safety Information (continued from first page)

Prescription CELEBREX should be used exactly as prescribed at the lowest dose possible and for the shortest time needed.

Do not take CELEBREX if you have had an asthma attack, hives, or other allergic reactions to aspirin, any other NSAID medicine, or certain drugs called sulfonamides.

Before you take CELEBREX, inform your healthcare provider of any medical conditions you may have and of all of the medications you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements as they may increase the risk for serious side effects. 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.

Tell your doctor about all of your medical conditions, including if you:

• have liver or kidney problems
• have a history of ulcers or bleeding in the stomach or intestines
• have high blood pressure or heart failure
• have asthma
• are pregnant or plan to become pregnant—CELEBREX, and other NSAIDs should not be taken in late pregnancy (after 29 weeks)
• are breastfeeding or plan to breast feed

CELEBREX can cause serious side effects, including:

• 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 allergic reactions
• life-threatening skin reactions

Other side effects of NSAIDs, including CELEBREX, are stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you have any of the following symptoms: shortness of breath or trouble breathing, chest pain, weakness in one part or side of your body, slurred speech, or swelling of the face or throat. Discontinue CELEBREX at first sign of skin rash, or blisters with fever.

Indications

CELEBREX is used to treat pain and redness, swelling, and heat (inflammation) from 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 menstrual cramps.

CELEBREX is available by prescription only in 50 mg, 100 mg, 200 mg, and 400 mg.

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)

RECENT MAJOR CHANGES

- Warnings and Precautions (5.4)
- Conditions and Usage
- Dosage and Administration
- Drug Interactions
- Use in Specific Populations

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)

DOSEAGE 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)

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

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers. (2.7, 8.6, 12.3)

DOSEAGE 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)

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, sinussitis, upper respiratory tract infection, rash (6.1).

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)

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
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

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For the management of the signs and symptoms of OA [see Clinical Studies (14.1)]

1.2 Rheumatoid Arthritis (RA)
For the management of the signs and symptoms of RA [see Clinical Studies (14.2)]

1.3 Juvenile Rheumatoid Arthritis (JRA)
For the management of the signs and symptoms of JRA in patients 2 years and older [see Clinical Studies (14.3)]

1.4 Ankylosing Spondylitis (AS)
For the management of the signs and symptoms of AS [see Clinical Studies (14.4)]

1.5 Acute Pain
For the management of acute pain in adults [see Clinical Studies (14.5)]

1.6 Primary Dysmenorrhea
For the management of primary dysmenorrhea [see Clinical Studies (14.5)]

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions
Carefully consider the potential benefits and risks of 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.

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

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

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

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

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2°C to 8°C/35°F to 45°F).

2.5 Ankylosing Spondylitis
For AS, the dosage of 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.

2.6 Management of Acute Pain and Treatment of Primary Dysmenorrhea
For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

2.7 Special Populations

Hepatic Impairment
In patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of 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 history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.

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

4. CONTRAINDICATIONS

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)]

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17. PATIENT COUNSELING INFORMATION

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

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 weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In the APC (Adenoma Prevention with Celecoxib) trial, there was an about fourfold 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 (APT), 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 patients in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

**Post-MI Patients**

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person-years in NSAID-treated patients compared to 12 per 100 person-years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

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

Complicated and symptomatic ulcer rates were 0.76% at nine months for all patients in the CLASS trial, and 4% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [see Clinical Studies (14.7)].

**Strategies to Minimize the GI Risks in NSAID-treated patients**:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider 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)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of patients treated with NSAIDs in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

In controlled clinical trials of CELEBREX, the incidence of bordereline 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 CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX 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), discontinue CELEBREX immediately, and perform a clinical evaluation of the patient.

5.4 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 angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

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

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, angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

In the CLASS study [see Clinical Studies (14.7)], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on 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 were 4.5%, 6.9% and 4.7%, respectively.

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.

CELEBREX is contraindicated in patients with severe heart failure. If CELEBREX is used in patients with severe heart failure, monitor patients for signs of new onset of heart failure or worsening of preexisting heart failure, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

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

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.
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 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>CELEBREX (CBX)</th>
<th>Placebo</th>
<th>NAP</th>
<th>DCF</th>
<th>IBU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>4.1%</td>
<td>2.8%</td>
<td>7.7%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.0%</td>
<td>1.7%</td>
<td>2.6%</td>
<td>1.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>15.8%</td>
<td>20.2%</td>
<td>14.5%</td>
<td>15.5%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.3%</td>
<td>2.3%</td>
<td>2.9%</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.3%</td>
<td>1.1%</td>
<td>1.7%</td>
<td>1.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.0%</td>
<td>2.4%</td>
<td>2.4%</td>
<td>2.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.0%</td>
<td>4.0%</td>
<td>4.0%</td>
<td>5.4%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8.1%</td>
<td>6.7%</td>
<td>9.9%</td>
<td>9.8%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>2.2%</td>
<td>2.1%</td>
<td>2.1%</td>
<td>1.3%</td>
<td>1.2%</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 due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.
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, hypertonia, 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):** Echymosis, epistaxis, thrombocytopenia

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

**Hemic:** 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

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, collitis 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 (≥3%) 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.

**Pre-Approval Studies**

**Adverse Reactions 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 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 as compared to the arthritis pre-marketing trials were as follows:

**CELEBREX (400 to 800 mg daily)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>N=2285</th>
<th>Celexib 3 mg/kg</th>
<th>Celexib 6 mg/kg</th>
<th>Naproxen 7.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>10.5%</td>
<td>7.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastroesophageal reflux disease</strong></td>
<td>4.7%</td>
<td>3.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>6.8%</td>
<td>5.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>3.2%</td>
<td>2.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>2.8%</td>
<td>1.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>12.5%</td>
<td>9.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nephrolithiasis</strong></td>
<td>2.1%</td>
<td>0.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:
Nervous system disorders: Cerebral infarction
Eye disorders: Vitreous floaters, conjunctival hemorrhage
Ear and labyrinth: Labyrinthitis
Cardiovascular disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy
Vascular disorders: Deep vein thrombosis
Reproductive system and breast disorders: Ovarian cyst
Investigations: Blood potassium increased, blood sodium increased, blood testosterone decreased
Injury, poisoning, and procedural complications: Epididymitis, tendon rupture

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of CELEBREX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Cardiovascular: Vasculitis, deep venous thrombosis
General: Anaphylactoid reaction, angioedema
Liver and biliary: Liver necrosis, hepatitis, jaundice, hepatic failure
Hemis and lymphatic: Agranulocytosis, aplastic anemia, pancytopenia, leucopenia
Metabolic: Hypoglycemia, hyponatremia
Renal: Interstitial nephritis

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 Interfere with Hemostasis</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of Celecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.</td>
<td>Monitor patients with concomitant use of CELEBREX with anticoagulants (e.g., warfarin), antplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding [see Warnings and Precautions (5.11)].</td>
<td></td>
</tr>
</tbody>
</table>

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 mg to 400 mg daily) has demonstrated a lack of interference with the cardioprotective antplatelet effect of aspirin (100 mg to 325 mg).

Intervention: Concomitant use of CELEBREX with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding.

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.

Intervention: During concomitant use of CELEBREX and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.

CYP2C9 Inhibitors or inducers

Clinical Impact: 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) 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.

Intervention: Concomitant use of CELEBREX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).

Table 3: Clinically Significant Drug Interactions with Celecoxib (cont’d)

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>During concomitant use of CELEBREX with diuretics, observe patients for signs of worsened renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].</td>
<td></td>
</tr>
</tbody>
</table>

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.

NSAIDs and Salicylates

Clinical Impact: Concomitant use of Celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)].

Intervention: The concomitant use of Celecoxib with other NSAIDs or salicylates is not recommended.

Pemetrexed

Clinical Impact: Concomitant use of CELEBREX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).

Intervention: During concomitant use of CELEBREX 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.

Intervention: Concomitant use of CELEBREX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).

Finally, the clinical impact of these interactions is to be considered, as well as the clinical benefit of the concomitant use of CELEBREX. Monitor patients with concomitant use of CELEBREX with diuretics, observe patients for signs of worsened renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].
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, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD. 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 AUC_{24h}) caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae 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 AUC_{24h} 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 ≥0.5 mg/kg/day (approximately 6 times human exposure based on the AUC_{24h} 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 AUC_{24h} 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 pauciarticular, polycyclic course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmaco kinetic, 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) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). When NSAIDs including celecoxib are used in patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see Dosage and Administration (2.4), Warnings and Precautions (5.12), 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), 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, 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) is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C₂₇H₂₄F₃N₂O₅S, and it has the following chemical structure:

Celecoxib 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 range. The inactive ingredients in CELEBREX include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium laurel sulfate.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Celecoxib 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 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 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 countering 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>Effective t1/2 (hr)</th>
<th>Vss/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.)

12.4 Special Populations

Gastrointestinal

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 decreases 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.

Racial

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 CELEBREX 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 CELEBREX 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 healthy subjects compared to Caucasians. The cause and clinical significance of this finding is unknown.
GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELEBREX 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 CELEBREX 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, ketonazole, [see Drug Interactions (7)], phenytoin, and tolbutamide have been studied in vivo and clinically important interactions have not been found.

### 12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 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/*3 genotypes. The pharmacogenetics 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 TOXICOLOGY

#### 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 AUC$_{24}$ at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC$_{24}$ at 200 mg twice daily) for two years.

**Mutagenesis**

Celecoxib was not mutagenic in Ames tests 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-fold human exposure based on the AUC$_{24}$ at 200 mg twice daily). At 50 mg/kg/day (approximately 6-times human exposure based on the AUC$_{24}$ at 200 mg twice daily) there was increased preimplantation loss.

#### 13.2 Animal Toxicology

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke with 80% power to evaluate non-inferiority. All patients were prescribed open-label ibuprofen, or 375 mg twice daily of naproxen, with the option of escalating the dose to 800 mg three times daily, and 54.8% (3946/7208) escalated to the 500 mg twice daily dose. Among subjects with RA, 55.7% (453/813) 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 the 200 mg twice daily dose, 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 trial had two prespecified analysis populations:

- Intent-to-treat population (ITT): Comprised of all randomized subjects followed for a maximum of 30 months.
- Modified Intent-to-treat population (mITT): Comprised of all randomized subjects who received at least one dose of study medication and had at least one post-baseline visit followed until the earlier of treatment discontinuation plus 30 days, or 43 months.

Celecoxib, at the 100 mg twice daily dose, as compared with either naproxen or ibuprofen at the doses taken, met all four prespecified non-inferiority criteria (p<0.001 for non-inferiority in both comparisons) for the APTC endpoint, a composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke [see Table 2]. Non-inferiority was prespecified as a hazard ratio (HR) of ≤1.12 in both ITT and mITT analyses, and upper 95% CI of ≤1.33 for ITT analysis and ≤1.40 for mITT analysis.

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

### Table 5. Primary Analysis of the Adjudicated APTC Composite Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<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>188 (2.3%)</td>
<td>218 (2.7%)</td>
<td>201 (2.5%)</td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td>Celecoxib vs. Naproxen</td>
<td>Celecoxib vs. Ibuprofen</td>
<td>Ibuprofen vs. Naproxen</td>
</tr>
<tr>
<td>HR (95% CI)</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>
</tr>
</tbody>
</table>

### Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8,030</td>
<td>7,990</td>
<td>7,933</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>Celecoxib vs. Naproxen</td>
<td>Celecoxib vs. Ibuprofen</td>
<td>Ibuprofen vs. Naproxen</td>
</tr>
<tr>
<td>HR (95% CI)</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>
</tbody>
</table>

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

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

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

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

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients at the celecoxib group, 1.8% in the ibuprofen group, and 2.0% in the naproxen group.

In the ITT analysis population through 30 months, all-cause mortality was 1.6% in this group. 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 NSAIIs 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 NSAIIs 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 study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low doses (≤ 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=3052). 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 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>Age</th>
<th>CELEBREX alone (n=3105)</th>
<th>CELEBREX with ASA (n=882)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 Years</td>
<td>0.78</td>
<td>2.19</td>
</tr>
<tr>
<td>≥65 Years</td>
<td>1.07</td>
<td>2.56</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) 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 the 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 were 4.5%, 6.9% and 4.7%, respectively.

The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen, and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively.

### 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)].
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>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1520-31</td>
<td>bottle of 100</td>
</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].
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 breastfeed.

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”, “antiplatelet drugs”, “anticoagulants”, “SSRIs” or “SNRIs”
- increasing doses of NSAIDs
- older age
- longer use of NSAIDs
- poor health
- smoking
- poor health
- 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 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 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.

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