Your Health Insurance Impacts Your Prescription Costs

The amount you pay for medical services and prescriptions is based on your health insurance plan. Use this guide to learn about insurance and how to get the brand-name medicine your doctor prescribed.

What is health insurance?

Health insurance is a type of insurance that helps cover medical services (doctor visits, hospital stays, lab tests, and preventative care) and prescription medicine expenses (costs of the medicines you take).

What is your insurance status?

<table>
<thead>
<tr>
<th>Private/Commercially Insured:</th>
<th>Medicare:</th>
<th>Medicaid:</th>
<th>Uninsured/Cash Paying:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offered by privately owned companies, often provided through an employer, the Affordable Care Act, or purchased on your own</td>
<td>Insurance offered by the government for people 65 years of age and older</td>
<td>Insurance offered by the government for people in need of financial aid</td>
<td>Healthcare expenses are paid out of your own pocket</td>
</tr>
</tbody>
</table>

Your health insurance may offer a prescription benefit which helps cover the cost of your prescription medicines.

How does my health insurance plan manage my prescription medicine benefits?

- **Formulary:** A drug formulary is a list of prescription drugs, both generic and brand name, that are preferred by your health plan. Drugs on formulary are usually grouped into tiers, and your cost is determined by the tier that applies to your medicine.

Can I get the brand-name medicine that my doctor prescribed even if it’s not preferred on formulary?

Yes, but your insurance may have additional requirements, such as:

- **Step edit:** Your doctor has to prove that you took a certain treatment without success before insurance will approve another medicine.

- **Prior authorization:** Your doctor must provide additional information (such as lab results or treatment history) before insurance will pay for your prescription.
From the Doctor to the Pharmacy: Steps to Getting Brand-Name Medicine

Pfizer is committed to helping you get the brand-name medicine your doctor prescribed.

**STEP 1: Doctor’s Office**

If your doctor feels medicine is the right option, they may prefer you take a brand-name medicine even if a generic is available.

**How can I ensure that I won’t get switched to a generic if my doctor wants me to take the brand-name medicine?**

Ask your doctor to include “No Generic Substitutions” or “DAW” (Dispense As Written) on your prescription, depending on your state’s requirements.

- “No Generic Substitutions” and “DAW” tell the pharmacist not to substitute a generic medication in place of the brand-name medicine your doctor prescribed.

Pfizer offers savings to help eligible patients save on brand-name medicine. Ask your doctor or the office staff for a savings offer before you leave the office, or visit the product website to view savings offers.

**STEP 2: Pharmacy Drop-Off**

At the pharmacy, give the pharmacist your brand-name prescription and savings offer.

**Can pharmacies switch my prescription from a brand name to a generic medicine?**

Yes, some pharmacies may switch your prescription from a brand name to a generic medicine if your doctor does not include “No Generic Substitutions” or “DAW”, per your state’s requirements, on your prescription.

Remember to show your Pfizer savings offer to the pharmacist when you fill your prescription. Let your pharmacist know that the savings offer only works with the brand-name medicine.

**STEP 3: Pharmacy Pickup**

When it’s time to pick up your prescription, check your pills. They should look the same every time you pick up a new refill.

**What should I do if I receive a generic substitute instead of the brand-name medicine?**

Talk to your pharmacist right away—let them know that you prefer to take the brand-name Pfizer medicine that your doctor prescribed.

Some pharmacies may substitute a generic for a brand-name medicine and may not let you know.

In need of prescription assistance?
Pfizer RxPathways® connects eligible patients to assistance programs that offer insurance support, co-pay assistance, and medicines for free or at a savings. Terms and conditions apply.

Learn more by visiting www.PfizerRxPathways.com or calling 1-844-989-PATH (7284).
WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL 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. (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)

USING 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.
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

1. INDICATIONS AND USAGE
   1.1 Osteoarthritis
   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
   2.2 Osteoarthritis
   2.3 Rheumatoid Arthritis
   2.4 Juvenile Rheumatoid Arthritis
   2.5 Ankylosing Spondylitis
   2.6 Management of Acute Pain and Treatment of Primary Dysmenorrhea
   2.7 Special Populations

3. DOSAGE FORMS AND STRENGTHS

4. CONTRAINDICATIONS

5. WARNINGS AND PRECAUTIONS

6. ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Postmarketing Experience

7. DRUG INTERACTIONS

8. USE IN SPECIFIC POPULATIONS

9. CLINICAL STUDIES

10. OVERDOSE

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

13. NONCLINICAL TOXICOLOGY

14. CLINICAL PHARMACOLOGY

15. CLINICAL STUDIES

16. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
3. DOSAGE 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 CABG surgery [see Warnings and Precautions (5.1)].
- In patients who have demonstrated allergic-type reactions to sulfonamides.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several 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 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 increase in CV events 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)].

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 without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Complicated and symptomatic ulcer rates were 0.76% at nine months for all patients in the CELEBREX trial and 2.4% in the non-COX-2 NSAID trial. In the subgroup of 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)].

The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for serious CV events over placebo for patients treated with celecoxib compared to placebo compared to patients treated with non-selective NSAIDs. The increase in CV events was observed most consistently at higher doses.

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

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)].

Heart Failure and Edema

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.
5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypervolemia, 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, dehydration or hypovolemia 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 hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions
Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. 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 (5.9)]. 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 erythropoesis. 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-morbidity 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 Infection 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)].

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 (%)</th>
<th>Placebo (%)</th>
<th>NAP (%)</th>
<th>DCF (%)</th>
<th>IBU (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Diarrhea</td>
<td>5.6</td>
<td>3.8</td>
<td>5.3</td>
<td>9.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.8</td>
<td>6.2</td>
<td>12.2</td>
<td>10.9</td>
<td>12.8</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.2</td>
<td>1.0</td>
<td>3.6</td>
<td>4.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.5</td>
<td>4.0</td>
<td>6.0</td>
<td>3.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>2.8</td>
<td>3.6</td>
<td>2.2</td>
<td>2.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>2.1</td>
<td>1.1</td>
<td>2.1</td>
<td>1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Injury-Accidental</td>
<td>2.9</td>
<td>2.3</td>
<td>3.0</td>
<td>2.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Central, Peripheral Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>Psychiatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.3</td>
<td>1.1</td>
<td>1.7</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.0</td>
<td>1.3</td>
<td>2.4</td>
<td>2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5.0</td>
<td>4.3</td>
<td>4.0</td>
<td>5.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>8.1</td>
<td>6.7</td>
<td>9.9</td>
<td>9.8</td>
<td>9.9</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</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 8.1% 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, hypertonita, 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, dysmenorrhea, 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 calculi  

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). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice daily had no observable deleterious effect on growth and development during the course of the 12-week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of JRA among treatment groups. In a 12-week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg twice daily. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Doses Twice Daily</th>
<th>Celecoxib 3 mg/kg N=77</th>
<th>Celecoxib 6 mg/kg N=82</th>
<th>Naproxen 7.5 mg/kg N=83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>64</td>
<td>70</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26</td>
<td>24</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain NOS</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diarrhea NOS</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>13</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>25</td>
<td>20</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Injury and Poisoning</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>3</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8</td>
<td>10</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td>17</td>
<td>11</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Headache NOS</td>
<td>13</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Dizziness (excl vertigo)</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>8</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10</td>
<td>7</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

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

Other Pre-Approval Studies

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

Adverse Events from Ankylosing Spondylitis Studies: Approximately 1,700 patients were treated with CELEBREX in ankylosis 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 ankylosis and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar ostelitis (dry socket) in the post-oral surgery pain studies.

The APC and PreSAP Trials

Adverse reactions from long-term, placebo-controlled polyv 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:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Doses Twice Daily</th>
<th>Celecoxib (400 to 800 mg daily) N = 2285</th>
<th>Placebo N=1303</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>10.5%</td>
<td>7.0%</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>4.7%</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8%</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.2%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>2.8%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.5%</td>
<td>9.8%</td>
<td></td>
</tr>
<tr>
<td>Necrotizingulosis</td>
<td>2.1%</td>
<td>0.8%</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 polyv 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 polyv prevention studies:
Table 3: Clinically Significant Drug Interactions with Celecoxib

### Drugs That Interfere with Hemostasis

**Clinical Impact:**
- Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of Celecoxib and anticoagulants has 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.

**Intervention:**
- Monitor patients with concomitant use of CELEBREX with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding [see Warnings and Precautions (5.11)].

### Aspirin

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

**Intervention:**
- Concomitant use of Celecoxib with aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.11)]. CELEBREX is not a substitute for low dose aspirin for cardiovascular protection.

### 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.
- 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.

### 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.

### 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.

- NSAIIDs 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 NSAIIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

### CYP2C9 Inhibitors or inducers

**Clinical Impact:**
- Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g., fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of celecoxib.

**Intervention:**
- Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers. [see Clinical Pharmacology (12.3)].
Table 3: Clinically Significant Drug Interactions with Celecoxib (cont’d)

<table>
<thead>
<tr>
<th>CYP2D6 substrates</th>
<th>Clinical Impact:</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6 (e.g., atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.</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 CYP2D6 substrates. [see Clinical Pharmacology (12.3)].</td>
</tr>
</tbody>
</table>

Corticosteroids

| Clinical Impact: | Monitor patients with concomitant use of CELEBREX with corticosteroids for signs of bleeding [see Warnings and Precautions (5.2)]. |

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Risk Summary

Use of NSAIDs, including 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, sternaebrae fused and sternaebrae 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, sternaebrae fused and sternaebrae 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.

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, 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 arthritis) were not recommended 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/*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)].

8.9 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 (5.4, 5.6)].
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 lauryl sulfate.

11. DESCRIPTION

CELEBREX (celecoxib) capsule is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C_{19}H_{18}F_{2}N_{4}O_{5}S, and it has the following chemical structure:

\[
\begin{align*}
\text{NH} & \quad \alpha \\
\text{CH}_2 & \quad \beta \\
\text{O} & \quad \alpha \\
\text{CF}_3 & \quad \beta
\end{align*}
\]

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\]

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 lauryl sulfate.

11. DESCRIPTION

CELEBREX (celecoxib) capsule is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C_{19}H_{18}F_{2}N_{4}O_{5}S, and it has the following chemical structure:

\[
\begin{align*}
\text{NH} & \quad \alpha \\
\text{CH}_2 & \quad \beta \\
\text{O} & \quad \alpha \\
\text{CF}_3 & \quad \beta
\end{align*}
\]
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)].

14.2 Rheumatoid Arthritis
CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg twice daily and 200 mg twice daily were similar in effectiveness and both were comparable to naproxen 500 mg twice daily.

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

14.3 Juvenile Rheumatoid Arthritis (NCT00652925)
In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 to 17 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with current active rheumatic 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 clinical response rates at week 12 were 89%, 86%, and 87% 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 Analog Scale), global disease activity (Visual Analog Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg CELEBREX doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to CELEBREX 200 mg, 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 surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses [see Dosage and Administration (2.6)] of CELEBREX provided pain relief within 60 minutes.

14.6 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 Trialists’ Collaboration (Aptc) composite, was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20-40 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% (3946/7208) escalated ibuprofen to 800 mg three times daily, and 54.6% (432/791) escalated naproxen 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 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.
Primary Endpoint
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>Intent-To-Treatment Analysis (ITT, through month 30)</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></td>
<td></td>
<td></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-Treatment Analysis (mITT, on treatment plus 30 days, through month 43)

<table>
<thead>
<tr>
<th>Intent-To-Treatment Analysis (mITT, through month 43)</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></td>
<td></td>
<td></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>Intent-To-Treatment Analysis (ITT, through month 30)</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>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-Treatment Analysis (mITT, 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>

*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

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 were 1.2% (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

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

Celecoxib Long-Term Arthritis Safety Study (CLASS)

This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months.

In the primary endpoint of this outcome study the incidence of complicated ulcers (gastrintestinal bleeding, perforation or obstruction) was 0.7% in the OA group and 1.2% in the RA group (difference 0.5% (0.0% - 1.0%), p = 0.21). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.92% for those on low-dose ASA and those not on ASA, respectively [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with CELEBREX 400 mg twice daily are displayed in Table 7. Table 7 also displays results for patients less than or greater than 65 years of age.

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 if 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)].
17. PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with CELEBREX until they talk to their healthcare provider [see Drug Interactions (7)].

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.
Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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”, “anticogulants”, “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 arthritis
- 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 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.