Studies show that staying active can ease arthritis symptoms. But if you have arthritis, staying active can be difficult. CELEBREX can help relieve arthritis pain so your body can stay in motion.

Important Safety Information:
All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods.

CELEBREX should not be used right before or after certain heart surgeries.

Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers.

Please see the full Prescribing Information including the Medication Guide that follows.
What is arthritis?

The word arthritis means “joint inflammation.” It describes more than 100 different diseases and conditions that affect joints, tissues that surround joints, and other connective tissue. The locations, types, and severity of symptoms can vary depending on the specific type of arthritis.

Unlike muscle pain, arthritis pain is primarily felt in and around joints. Symptoms of arthritis include pain, stiffness, swelling, and a decreased range of motion.

Arthritis is common in adults 65 and older. But it can affect people of all ages, races, and ethnic groups. The two most common forms of arthritis are osteoarthritis and rheumatoid arthritis.

Quick fact about arthritis

• One out of every 5 adults in the U.S. has reported some form of doctor-diagnosed arthritis.
Osteoarthritis (OA)

OA is a disease that accounts for more than 50% of arthritis cases in the U.S., making it the most common form of arthritis. While the cause of OA is unknown, it occurs when cartilage between the joints begins to break down over time. Often called “wear and tear” arthritis, OA is commonly found in the knees, hips, hands, or spine, though it can occur in any joint.

Symptoms of OA include:

- A feeling of pain in or around the joint
- Tenderness and stiffness in the joint
- Loss of flexibility or range of motion
- Grating sensation or sound in the joint, known as crepitus

Quick facts about OA

- One in two people in the U.S. will experience some form of OA in their lifetime.
- OA affects about 27 million Americans over the age of 25.

Normally, the ends of the bones in a joint are cushioned by cartilage. In this example of a knee with osteoarthritis, a joint commonly affected by OA, the cartilage thins out, and the ends of the bones become exposed to each other and rub together. This can damage the bones with pain and decreased range of motion in the knee. Bone spurs, or bony projections, can also develop along the joint, which can also cause pain when extending or bending the knee.
Rheumatoid arthritis (RA)
RA is an autoimmune disease. An autoimmune disease is when the body’s defense system malfunctions and begins to mistakenly attack itself. In RA, the body attacks its own tissues, membranes, and ligaments that surround a joint, eventually destroying the joint itself. RA is approximately 3 times more common in women than in men. It typically affects the smaller joints of the hands and feet, but, in some cases, it can affect other parts of the body such as the lungs, eyes, and blood vessels.

Symptoms of RA include:
• Pain and swelling of joints
• Joints that are tender to the touch
• Red and puffy joints

• Morning joint stiffness
• Fever, fatigue, and loss of appetite
• Bumps under the skin (called rheumatoid nodules)

Quick facts about RA
• Like OA, the primary symptom of RA is felt in and around the joints.
• RA can start developing as early as age 20.

In this example of a knee with rheumatoid arthritis, there is a swelling and thickening of the synovial membrane, the connective tissue that lines the joint cavity and produces fluid to lubricate the joint. There is also loss of the cartilage and bone. All of this can result in pain.
Treating arthritis

Staying active can actually relieve arthritis symptoms. But if you have arthritis, staying active can be difficult. And, while there’s no way to reverse the cartilage loss of arthritis, your doctor may recommend steps you can take to manage the arthritis pain and inflammation. These steps can include diet, exercise, or alternative therapies — in addition to a medication like CELEBREX.

So talk to your doctor about treatment options, like prescription CELEBREX.

Important Safety Information:

All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods.

CELEBREX should not be used right before or after certain heart surgeries.

Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers.

Please see the full Prescribing Information including the Medication Guide that follows.
What is CELEBREX?

CELEBREX is FDA approved to treat the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and for the management of acute pain in adults. It is a prescription NSAID, or nonsteroidal anti-inflammatory drug. CELEBREX is not a narcotic.

Benefits of CELEBREX

• Just one 200-mg CELEBREX a day can provide 24-hour relief for many with arthritis pain and inflammation.*

• In clinical studies with osteoarthritis patients, CELEBREX is proven to improve daily physical function, so moving is easier.

• In fact, CELEBREX improves pain, stiffness, and physical function.

Like all medications, there are potential risks and side effects that you should be aware of before taking CELEBREX. CELEBREX should always be taken as your doctor prescribes.

* Individual results may vary. This dosing is for osteoarthritis.

Did you know?

CELEBREX can be taken with or without food, so you don’t have to plan your day around it.

Important Safety Information:

Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers.

Life threatening allergic reactions can occur with CELEBREX. Get help right away if you’ve had swelling of the face or throat or trouble breathing.

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

Please see the full Prescribing Information including the Medication Guide that follows.
Other reasons your doctor may prescribe CELEBREX to help relieve your arthritis symptoms

In clinical studies, a lower percentage of patients taking CELEBREX reported stomach discomfort (including indigestion, abdominal pain, and nausea) versus those taking prescription ibuprofen and naproxen.

CELEBREX doesn’t interfere with aspirin. If you’re taking low-dose aspirin for your heart and need an NSAID pain reliever, CELEBREX can be used because it doesn’t interfere with aspirin’s antiplatelet effect. However, taking low-dose aspirin may not reduce the cardiovascular risk associated with NSAID use.

When it comes to relieving your arthritis pain, you and your doctor need to balance the benefits and the risks.

Ask your doctor if CELEBREX is right for you.

Did you know?

Prescription CELEBREX has been the option for millions of patients for over 10 straight years.

Important Safety Information

Tell your doctor if you have a history of ulcers or bleeding in the stomach or intestines, high blood pressure or heart failure, or kidney or liver problems.

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

Please see the full Prescribing Information including the Medication Guide that follows.
How CELEBREX works.

The human body contains enzymes that facilitate chemical reactions in the body. One of these enzymes is cyclooxygenase-2 (COX-2), which is involved in causing inflammation and pain in parts of the body where there is arthritis or injury.

CELEBREX at recommended doses selectively inhibits COX-2, which helps relieve arthritis pain and inflammation, as well as acute pain in adults.

Important Safety Information

CELEBREX should not be taken in late pregnancy.

Please see the full Prescribing Information including the Medication Guide that follows.
Partnering with your doctor.

One of the most valuable resources you have in managing your arthritis is your doctor. He or she can help find the right medication for you and also recommend additional treatment that best suits your needs.

When you schedule an appointment, be prepared to talk about what you’ve been doing to manage your arthritis pain, along with your medical and lifestyle history. Make a list of all medical conditions you have and medicines you are currently taking.

As part of your arthritis treatment, it’s important to take CELEBREX® (celecoxib) Capsules as your doctor prescribes. Make sure to schedule follow-up appointments and keep your doctor informed of your progress or any side effects you may experience.

Take advantage of our Doctor Discussion Guide.

Use the Doctor Discussion Guide at the end of this PDF to create a personalized guide that can help you discuss your arthritis pain and potential treatment options with your doctor.

Important Safety Information

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

Please see the full Prescribing Information including the Medication Guide that follows.
Managing your arthritis pain with an integrated approach.

Managing arthritis is about a combination of ideas and tools in addition to taking your medication. With these important steps, you can continue to take an active role in your treatment.

**Education**
Staying informed of the latest news and discovering new tips about arthritis can help you find new ways to manage the pain.

**Staying Active**
Staying active can ease arthritis symptoms so moving is easier. Studies show that certain types of exercise, like light aerobics, strength training, range-of-motion exercise, and yoga can actually help relieve arthritis pain.

**Nutrition**
Maintaining a healthy diet is important. Better eating can help you maintain a proper weight, which may lessen the impact on your joints. In fact, for every pound of weight loss, 4 pounds of stress is taken off your knee joint.

**Lifestyle**
Adapting things you use in your daily life can help improve your ability to perform everyday tasks. Using arthritis-friendly tools like a special trowel for gardening or elastic shoelaces to make putting on shoes easier can help protect your joints from painful moves.

**Medication**
Guidelines suggest that you follow an integrated approach to arthritis pain management that combines a medication with other recommended therapies.

**Partnering with your doctor**
Your doctor is an important part of your arthritis treatment. Be sure to keep him or her informed of your progress and any side effects you might have.
**Indications:**

CELEBREX® (celecoxib) Capsules is indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and for the management of acute pain in adults.

**Important Safety Information:**

All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods.

CELEBREX should not be used right before or after certain heart surgeries.

Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers.

Tell your doctor if you have:

- A history of ulcers or bleeding in the stomach or intestines
- High blood pressure or heart failure
- Kidney or liver problems

CELEBREX should not be taken in late pregnancy.

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

Life threatening allergic reactions can occur with CELEBREX. Get help right away if you’ve had swelling of the face or throat or trouble breathing.

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

*Please see the full Prescribing Information including the Medication Guide that follows.*
Doctor Discussion Guide

This guide is designed to help you discuss your arthritis pain and potential treatment options with your doctor. Answer the following questions as best you can and note the places where you have questions so that you can ask your doctor about them during your next appointment.

Step 1

1) Locate the areas where you feel arthritis pain by filling in the circle(s).

Rate your arthritis pain.

- ○ Mild  ○ Moderate  ○ Severe  ○ Extreme

2) Is this a new arthritis pain?

- ○ Yes  ○ No

(If No, is this arthritis pain worse than it was 3 months ago?)

- ○ Yes  ○ No

Step 2

3) Please list any medications you are currently taking:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

4) Please select any of the following you're using to find relief from your arthritis pain. (Select all that apply.)

- ○ Pain relievers
- ○ Heating pads or ice packs
- ○ Resting/Not using that area
- ○ Light activity or exercise
- ○ Other

5) Are you currently taking low-dose aspirin for your heart?

- ○ Yes  ○ No
Step 3

These topics can help your doctor understand your arthritis pain. Select which ones you’d like to discuss.

- Sharp vs dull pain
- Local vs allover pain
- Consistent vs intermittent pain
- Pain in the same place on both sides of the body
- Worst time of day for pain (i.e., morning, night)
- Previous injuries

Here are some questions you might want to ask your doctor. Select the ones you’d like to ask.

- What could be the cause of my joint pain?
- With my medical history, is CELEBREX® (celecoxib) Capsules the right treatment for me?
- In addition to medicine, what other treatment options might help?
- Can CELEBREX be taken with low-dose aspirin?

The next step is talking to your doctor.

Take this Doctor Discussion Guide with you when you go to your next appointment.

**Indications:**

CELEBREX is indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and for the management of acute pain in adults.

**Important Safety Information:**

All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods.

CELEBREX should not be used right before or after certain heart surgeries.

Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers.

Tell your doctor if you have:

- A history of ulcers or bleeding in the stomach or intestines
- High blood pressure or heart failure
- Kidney or liver problems

CELEBREX should not be taken in late pregnancy.

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

Life threatening allergic reactions can occur with CELEBREX. Get help right away if you’ve had swelling of the face or throat or trouble breathing.

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

*Please see the full Prescribing Information including the Medication Guide that follows.*
CELEBREX® (celecoxib) capsules

Use lowest effective dose for the shortest duration consistent with treatment goals for the individual patient. (1, 5.1, 5.4)
- OA: 200 mg once daily or 100 mg twice daily (2.1, 14.1)
- RA: 100 to 200 mg twice daily (2.2, 14.2)
- JRA: 50 mg twice daily in patients 10-25 kg, 100 mg twice daily in patients more than 25 kg (2.3, 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 (2.4, 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 (2.5, 14.5)
Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B).
Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers, (2.6, 8.4, 8.8, 12.3).

Dosage Forms and Strengths
Capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)
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* Sections or subsections omitted from the Full Prescribing Information are not listed.
INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see Warnings and Precautions (5)).

Osteoarthritis (OA)

CELEBREX is indicated for relief of the signs and symptoms of OA [see Clinical Studies (14.1)].

Rheumatoid Arthritis (RA)

CELEBREX is indicated for relief of the signs and symptoms of RA [see Clinical Studies (14.2)].

Juvenile Rheumatoid Arthritis (JRA)

CELEBREX is indicated for relief of the signs and symptoms of JRA in patients 2 years and older [see Clinical Studies (14.3)].

Ankylosing Spondylitis (AS)

CELEBREX is indicated for the relief of signs and symptoms of AS [see Clinical Studies (14.4)].

Acute Pain (AP)

CELEBREX is indicated for the management of AP in adults [see Clinical Studies (14.5)].

DOSAGE AND ADMINISTRATION

Use lowest effective dose for the shortest duration consistent with treatment goals for the individual patient. These doses can be given without regard to timing of meals.

Osteoarthritis

For relief of the signs and symptoms of OA the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice daily.

Rheumatoid Arthritis

For relief of the signs and symptoms of RA the recommended oral dose is 100 to 200 mg twice daily.

Juvenile Rheumatoid Arthritis

For the relief of the signs and symptoms of JRA the recommended oral dose 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 (2-8°C/35-45°F).

Ankylosing Spondylitis

For the management of the signs and symptoms of AS, the recommended dose of CELEBREX is 200 mg daily in single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of CELEBREX is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Special Populations

Hepatic insufficiency: 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 Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

Poor Metabolizers of CYPC29 Substrates: Patients who are known or suspected to be poor CYPC29 metabolizers based on genotype or previous history/experience with other CYPC29 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider switching treatment at half the lowest recommended dose in poor metabolizers (i.e. CYPC29*3/*3). Consider using alternative management in JRA patients who are poor metabolizers. [See Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].

Dosage Forms and Strengths

Capsules: 50 mg, 100 mg, 200 mg and 400 mg

Contraindications

CELEBREX is contraindicated:

- In patients with known hypersensitivity to celecoxib, aspirin, or other NSAIDs.
- In patients who have demonstrated allergic-type reactions to sulfonamides.
- In patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactoid reactions to NSAIDs, some of them fatal, have been reported in such patients [see Warnings and Precautions (5.7, 5.13)].
- For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)].

Warnings and Precautions

Cardiovascular Thrombotic Events

Chronic use of CELEBREX may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the ACR (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 2.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/665 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [see Clinical Studies (14.6)].

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with CELEBREX, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, especially during treatment and during reinitiation of therapy with CELEBREX and throughout the course of therapy. 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 [see Clinical Studies (14.6)].

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

Hypertension

As with all NSAIDs, CELEBREX can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including CELEBREX, should be used with caution in patients with hypertension and should be monitored carefully during the initiation of therapy with CELEBREX and throughout the course of therapy. The rate of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 4.7%, respectively. CELEBREX should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects

Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including CELEBREX, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the 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 NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [see Clinical Studies (14.6)]. With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID use, heavy smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during CELEBREX therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.
5. Hepatic Effects
Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CLEVEREX [see Adverse Reactions (6.1)]. In controlled clinical trials of CLEVEREX, the incidence of border-line 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 CLEVEREX and 5% for placebo, and approximately 0.2% of patients taking CLEVEREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CLEVEREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CLEVEREX should be discontinued.

5. Renal Effects
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, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CLEVEREX have shown renal effects similar to those observed with comparator NSAIDs.

No information is available from controlled clinical studies regarding the use of CLEVEREX in patients with advanced renal disease. Therefore, treatment with CLEVEREX is not recommended in these patients with advanced renal disease. If CLEVEREX therapy must be initiated, close monitoring of the patient’s renal function is advisable.

5.12 Disseminated Intravascular Coagulation (DIC)
Because serious GI tract ulcers and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, CLEVEREX should be discontinued. In controlled clinical trials, elevated BU N occurred more frequently in patients receiving CLEVEREX 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.

5.15 Inflammation
The pharmacological activity of CLEVEREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

5.16 Concomitant NSAID Use
The concomitant use of CLEVEREX with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

6. ADVERSE REACTIONS
Of the CLEVEREX-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 CLEVEREX 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 CLEVEREX 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.
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.

6.1 Pre-marketing Controlled Arthritis Trials
Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CLEVEREX 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 CLEVEREX Patients from Pre-marketing Controlled Arthritis Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>CBX N=4146</th>
<th>Placebo N=1864</th>
<th>NAP N=1366</th>
<th>DCF N=387</th>
<th>IBU N=345</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>5.5%</td>
<td>3.8%</td>
<td>5.3%</td>
<td>9.3%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8.8%</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>4.2%</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 = CLEVEREX 100 – 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 CLEVEREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CLEVEREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 8% and 7% of CLEVEREX patients, respectively). Among patients receiving placebo, 0.5% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

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

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

Cardiovascular:
- Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General:
- Allergy aggravated, 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, hyposthesia, migraine, paresthesia, vertigo
6.2 The Celecoxib Long-Term Arthritis Safety Study

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 ASA 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).

6.3 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 BID, 82 patients were treated with celecoxib 6 mg/kg BID, and 83 patients were treated with naproxen 7.5 mg/kg BID. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhoea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhoea, cough, abdominal pain, and dizziness (Table 2). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg BID 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 BID. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

### Table 2: Adverse Events Occurring in ≥5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>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>
</tr>
<tr>
<td>Eye Disorders</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26%</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td>General</td>
<td>13%</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8%</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10%</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>3 mg/kg</td>
<td>6 mg/kg</td>
<td>7.5 mg/kg</td>
</tr>
<tr>
<td>N=77</td>
<td>N=82</td>
<td>N=83</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</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>Dyspea</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>
</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, Hemocrit decreased, Hematocrit present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS.

6.4 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/RAS 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.

6.5 The APC and PreSAP Trials

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

**CELEBREX**

(400 to 800 mg daily) N = 2285

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo N = 1303</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>10.5%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>4.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.2%</td>
</tr>
<tr>
<td>Dyspea</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.5%</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
- **Cardiac 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

Deafness, tinnitus

Palpititation, tachycardia

Hepatic function abnormal, SGOT increased, SGPT increased

BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Arthralgia, arthritis, myalgia, synovitis, tendinitis

Hemorrhage [see Drug Interactions (7.1)]

Alopecia, dermatitis, photosensitivity reaction, pruritus, rash
edry erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Cardiac disorders:

Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders:

Deep vein thrombosis

Mucosal disorders:

Arthralgia, arthropathy, myalgia, synovitis, tendinitis

Liver and biliary:

Hepatitis, jaundice, liver failure

Musculoskeletal:

Arthralgia, arthropathy, myalgia, synovitis, tendinitis

Hemic:

Hematology:

Anemia, leucopenia, neutropenia

Skin:

Skin and appendages:

Eczematous dermatitis, pruritus, rash

Respiratory:

Respiratory, cardiovascular:

Cardiomegaly, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis, deep vein thrombosis

Gastrointestinal:

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

Cardiovascular:

Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis, deep vein thrombosis

Metabolic:

BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Liver and biliary:

Hepatitis, jaundice, liver failure

Musculoskeletal:

Arthralgia, arthritis, myalgia, synovitis, tendinitis

Hemic:

Anemia

Respiratory:

Bronchitis, bronchospasm, bronchospasm aggravated, coughing, 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 (cases reported only in post-marketing experience are indicated in Italics):

**Cardiovascular:**

Syncpe, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis, deep vein thrombosis

**Gastrointestinal:**

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

**Liver and biliary:**

Cholelithiasis, hepatitis, jaundice, liver failure

**Hemic and lymphatic:**

Thrombocytopenia, agranulocytosis, aplastic anemia, pancytopenia, leucopenia

**Metabolic:**

Hyperglycemia, hypoglycemia

**Nervous:**

Ataxia, suicidal, aetiology, meningitis, ageusia, anosmia, fatal intracranial hemorrhage (see Drug Interactions (7.1)).

**Renal:**

Acute renal failure, interstitial nephritis

**Skin:**

Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome)

**General:**

Sepsis, sudden death, anaphylactoid reaction, angioedema
7.1 Pregnancy

Pregnancy Category C. Pregnancy category D from 30 weeks of gestation onward. Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of Celecoxib in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year-old child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when Celecoxib is administered to a nursing woman.

7.2 Lithium

Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with Celecoxib increases the rate of GI ulceration or other complications, compared to use of Celecoxib alone (see Warnings and Precautions). Celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

7.3 Aspirin

Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with Celecoxib increases the rate of GI ulceration or other complications, compared to use of Celecoxib alone (see Warnings and Precautions). Celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

7.4 ACE-inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking Celecoxib concomitantly with ACE-inhibitors and angiotensin II antagonists (see Clinical Pharmacology).

7.5 Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via CYP450 CYP2C9 by fluconazole (see Clinical Pharmacology).

7.6 Furosemide

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

7.7 Methotrexate

In an interaction study of rheumatoid arthritis patients taking methotrexate, Celecoxib did not have an effect on the pharmacokinetics of methotrexate (see Clinical Pharmacology). Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

7.8 Concomitant NSAID Use

The concomitant use of Celecoxib with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC_{0-24}) caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternum fused and sternum mesenchapse 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-fold human exposure based on the AUC_{0-24} at 200 mg twice daily) throughout organogenesis. There are no studies in pregnant women. Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral doses ≥50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of Celecoxib during the third trimester of pregnancy should be avoided.

8.2 Labor and Delivery

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_{0-24} at 200 mg BID). The effects of Celecoxib on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of Celecoxib in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year-old child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when Celecoxib is administered to a nursing woman.

8.4 Pediatric Use

Celecoxib 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 Celecoxib has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to Celecoxib or other COX-2 selective and non-selective NSAIDs (see Boxed Warning, Warnings and Precautions). The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, placebo, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). NSAIDs including celecoxib should be used only with caution in patients with systemic onset JRA, 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 (2.3), 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

Of the total number of patients who received Celecoxib 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).

8.6 Hepatic Insufficiency

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

8.7 Renal Insufficiency

Celecoxib is not recommended in patients with severe renal insufficiency (see Warnings and Precautions). 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) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3).

8.8 Poor Metabolizers of CYP2C9 Substrates

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) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3).
Celecoxib oral capsules contain either 50 mg, 100 mg, 200 mg or 400 mg of celecoxib, together with inactive ingredients including: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.

11. DESCRIPTION
Celecoxib (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-( trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is C₃₇H₂₁F₃N₂O₅S, and the molecular weight is 681.38; the chemical structure is as follows:

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, Celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, Celecoxib reduced the incidence and multiplicity of tumors.

12.2 Pharmacokinetics
Platelets: In clinical trials using normal volunteers, Celecoxib 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, Celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of Celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of Celecoxib.

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

12.3 Pharmacokinetics
Absorption: Peak plasma levels of celecoxib occur approximately 3 hrs 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 BID; 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 3.

Table 3
Summary of Single Dose (200 mg) Disposition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (CV) PK Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>2.8 (31)</td>
</tr>
<tr>
<td>Tmax, hr</td>
<td>11.2 (31)</td>
</tr>
<tr>
<td>t1/2, hr</td>
<td>429 (34)</td>
</tr>
<tr>
<td>CL/F, L/hr</td>
<td>27.7 (32)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (~3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radioabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life (t1/2) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose [see Dosage and Administration (2.6) and Use in Specific Populations (8.5)].

Pediatric: The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polycarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient.

Twice-daily administration of 50 mg capsules to JRA patients weighing ≥12 to ≤25 kg and 100 mg capsules to JRA patients weighing ≥25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily [see Dosage and Administration (2.3)].

Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.

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

Hepatic Insufficiency: 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 Celecoxib 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 Celecoxib in patients with severe hepatic impairment is not recommended [see Dosage and Administration (2.6) and Use in Specific Populations (8.6)].

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, Celecoxib is not recommended in patients with severe renal insufficiency [see Warnings and Precautions (5.6)].

Drug Interactions:
In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9.

In vivo studies have shown the following:
Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with Celecoxib 200 mg twice daily as compared to subjects receiving lithium alone [see Drug Interactions (7.2)].

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 (7.5)].

Other Drugs: The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketocazole, metohotrexate [see Drug Interactions (7.7)], 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 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% 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
Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC0-24h at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC0-24h at 200 mg twice daily) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosone aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg twice daily based on the AUC0-24h).
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 what was seen with 100-200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis

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

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

14.4 Ankylosing Spondylitis

CELEBREX was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg CELEBREX doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to CELEBREX 400 mg, 53%, than to CELEBREX 200 mg, 44%, using the ASAS 40 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-surgical pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses [see Dosage and Administration (2.5)] of CELEBREX provided pain relief within 60 minutes.

14.6 Special Studies

Adenomatous Polyp Prevention Studies

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

In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to placebo (2.0% (13/658 subjects)) with placebo group. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.

In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 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% (12/638 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.

CELEBREX Long-Term Arthritis Safety Study (CLASS): This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on CELEBREX and concomitant low-dose ASA (n=882) experienced 4-fold higher rates of complicated ulcers compared to patients not on ASA (n=310). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively [see Warnings and Precautions (5.4)]. The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with CELEBREX 400 mg twice daily are described in Table 4. Table 4 also displays results for patients less than or greater than 65 years of age. The difference in rates between CELEBREX alone and ASA groups may be due to the higher risk for GI events in ASA users.

Table 4: 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>Risk Factor</th>
<th>All Patients</th>
<th>Patients ≤65 Years</th>
<th>Patients &gt;65 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELEBREX alone (n=3105)</td>
<td>0.78</td>
<td>0.60</td>
<td>0.96</td>
</tr>
<tr>
<td>CELEBREX with ASA (n=882)</td>
<td>2.19</td>
<td>1.37</td>
<td>3.02</td>
</tr>
<tr>
<td>CELEBREX alone (n=2025)</td>
<td>0.47</td>
<td>0.40</td>
<td>0.53</td>
</tr>
<tr>
<td>CELEBREX with ASA (n=403)</td>
<td>1.26</td>
<td>1.13</td>
<td>1.39</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 6.83% (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 patients at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA patients at nine months in each of the three treatment groups were less than 0.1%. CELEBREX was not the placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

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

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial [see Clinical Studies (14.6)]. The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled 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 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:

- **NDC Number** 0025-1515-01 bottle of 60
- **NDC Number** 0025-1520-31 bottle of 100
- **NDC Number** 0025-1520-51 bottle of 500
- **NDC Number** 0025-1520-34 carton of 100 unit dose

Celebrex 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:

- **NDC Number** 0025-1525-01 bottle of 60
- **NDC Number** 0025-1525-51 bottle of 500
- **NDC Number** 0025-1525-34 carton of 100 unit dose

Celebrex 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:

- **NDC Number** 0025-1530-01 bottle of 60
- **NDC Number** 0025-1530-02 bottle of 60
- **NDC Number** 0025-1530-01 carton of 100 unit dose

**Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

17. **PATIENT COUNSELING INFORMATION**

Patients should be informed of the following information before initiating therapy with Celebrex and periodically during the course of ongoing therapy.

17.1 **Medication Guide**

Patients should be informed of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and should be instructed to read the Medication Guide prior to using Celebrex.

17.2 **Cardiovascular Effects**

Patients should be informed that Celebrex may cause serious CV side effects such as MI or stroke, which may result in hospitalization and even death. Patients should be informed of the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to seek immediate medical advice if they observe any of these signs or symptoms. [see Warnings and Precautions (5.1)].

Patients should be informed that Celebrex can lead to the onset of new hypertension or worsening of preexisting hypertension, and that Celebrex may impair the response of some antihypertensive agents. Patients should be instructed on the proper follow up for monitoring of blood pressure. [see Warnings and Precautions (5.2) and Drug Interactions (7.4)].

17.3 **Gastrointestinal Effects**

Patients should be informed that Celebrex can cause gastrointestinal discomfort and more serious side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Patients should be informed of the signs and symptoms of ulcerations and bleeding, and to seek immediate medical advice if they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. [see Warnings and Precautions (5.4)].

17.4 **Hepatic Effects**

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur [see Warnings and Precautions (5.5), Use in Specific Populations (8.6)].

17.5 **Adverse Skin Reactions**

Patients should be informed that Celebrex is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be informed of the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and seek immediate medical advice when observing any indicative signs or symptoms. Patients should be advised to stop Celebrex immediately if they develop any type of rash and contact their physician as soon as possible. Patients with prior history of sulfa allergy should not take Celebrex [see Warnings and Precautions (5.8)].

17.6 **Weight Gain and Edema**

Long-term administration of NSAIDs including Celebrex has resulted in renal injury. Patients at greatest risk are those taking diuretics, ACE-inhibitors, angiotensin II antagonists, or with renal or liver dysfunction, heart failure, and the elderly [see Warnings and Precautions (5.3, 5.6), Use in Specific Populations (8)].

Patients should be instructed to promptly report to their physicians signs or symptoms of unexplained weight gain or edema following treatment with Celebrex [see Warnings and Precautions (5.3)].

17.7 **Anaphylactoid Reactions**

Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms [see Warnings and Precautions (5.7)].

17.8 **Effects During Pregnancy**

Patients should be informed that in late pregnancy Celebrex should be avoided because it may cause premature closure of the ductus arteriosus [see Warnings and Precautions (5.9), Use in Specific Populations (8.1)].

17.9 **Preexisting Asthma**

Patients should be instructed to tell their physicians if they have a history of asthma or aspirin-sensitive asthma because the use of NSAIDs in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Patients with this form of aspirin sensitivity should be instructed not to take Celebrex. Patients with preexisting asthma should be instructed to seek immediate medical attention if their asthma worsens after taking Celebrex [see Warnings and Precautions (5.13)].

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**Medication Guide**

for **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

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

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:
- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAIDs are medicines 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 a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:
- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. Keep a list of your medicines to show to your healthcare provider and pharmacist.
- if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy.
- if you are breastfeeding. Talk to your doctor.

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

**Serious side effects include:**
- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

**Other side effects include:**
- stomach pain
- constipation
- diarrhea
- gas
- heartburn
- nausea
- vomiting
- 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
- swelling of the face or throat

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

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine 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 of these NSAID medicines 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.

**NSAID medicines that need a prescription**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Tradename</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Cataflam, Voltaren, Arthrotec (combined with misoprostol)</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Dolobid</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Lodine, Lodine XL</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Nalfon, Nalfon 200</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocin, Indocin SR, Indo-Lemmon, Indomethagan</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Oruvail</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Toradol</td>
</tr>
<tr>
<td>Mefenamic Acid</td>
<td>Ponstel</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Mobic</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Relafen</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Daypro</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Clinoril</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Tolectin, Tolectin DS, Tolectin 600</td>
</tr>
</tbody>
</table>

* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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