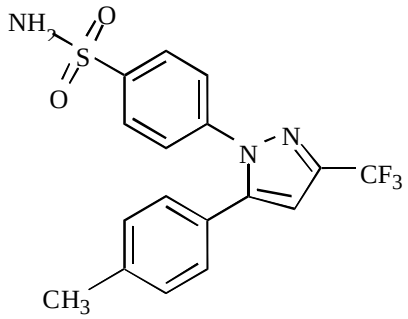
CELEBREX™
(celecoxib capsules)

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional across the clinical dose range of 100-200 mg studied. At higher doses, under fasting conditions, there is a less than proportional increase in Cmax and AUC which is thought to be due to the low solubility of the drug in aqueous media. Because of the low

solubility, 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 1.

Table 1: Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
Cmax, ng/mL	**Tmax, hr**	**Effective t1/2, hr**	**Vss/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

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

Food Effects

When CELEBREX 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%. Coadministration of CELEBREX 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. CELEBREX capsules can be administered without regard to the timing of meals.

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, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/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 cytochrome P450 2C9. 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. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) 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.

Special Populations

Geriatric

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

Pediatric

CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

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 I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, CELEBREX capsules should be introduced at a reduced dose in patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

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.

Drug Interactions

Also see **PRECAUTIONS – Drug Interactions.**

General: Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of

celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, tolbutamide, and warfarin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA): CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100mg BID and 200mg BID provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA): 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 approximately 2,100 patients 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 BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

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

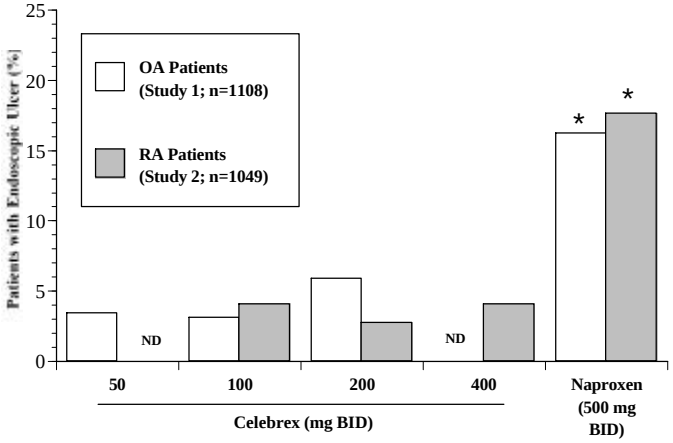
Special Studies

***Gastrointestinal**:* Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24 week endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from 50-400 mg BID. In all three studies that included naproxen 500 mg BID, and in the study that included ibuprofen 800 mg TID, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared CELEBREX with diclofenac 75 mg BID; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant

difference between cumulative endoscopic ulcer incidence rates in the diclofenac and CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Figure 1 and Table 2 summarize the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Figure 1
Incidence of Endoscopically Observed Gastroduodenal Ulcers after Twelve Weeks of Treatment



ND = Not Done

* Significantly different from all other treatments; $p<0.05$.

Celebrex 100 mg BID and 200 mg QD, BID are the recommended doses. These studies were not powered to compare the endoscopic ulcer rates of Celebrex vs. placebo.

Study 1: placebo ulcer rate = 2.3%
Study 2: placebo ulcer rate = 2.0%

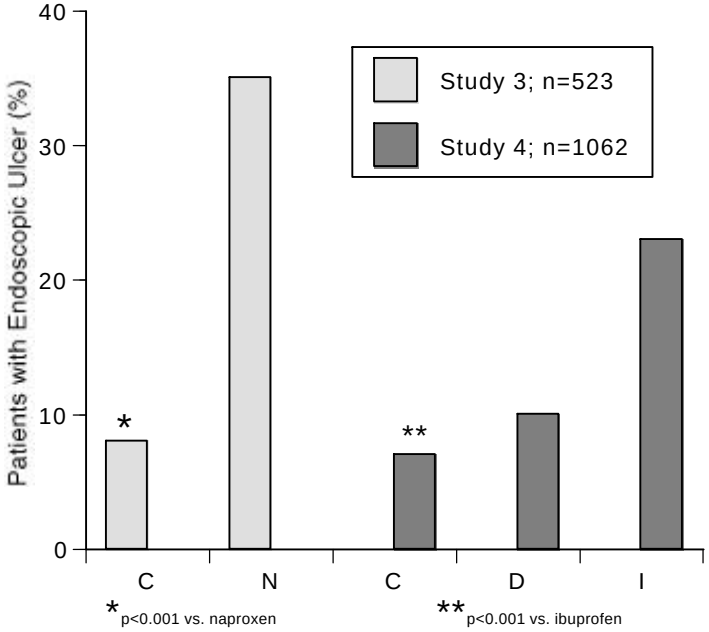
Table 2
Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

	3 Month Studies	
	Study 1 (n = 1108)	**Study 2 (n= 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

Figure 2 and Table 3 summarize data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Figure 2
Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies Over 12 Weeks



C = Celecoxib 200 mg BID D = Diclofenac 75 mg BID
N = Naproxen 500 mg BID I = Ibuprofen 800 mg TID

Table 3
Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
Celebrex 200 mg BID	4.0% (10/252)*	2.2% (5/227)	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
Celebrex 200 mg BID	3.9% (13/337)†	2.4% (7/296)†	1.8%(5/274)†	7.0% (25/356)†
Diclofenac 75 mg BID	5.1% (18/350)	3.3% (10/306)	2.9%(8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

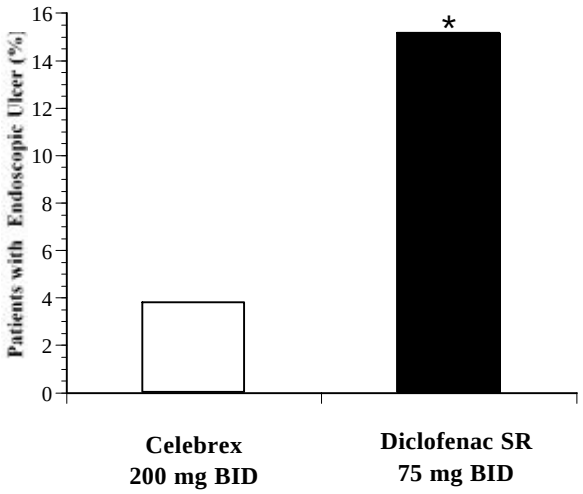
*p≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses
† p≤ 0.05 Celebrex vs. ibuprofen based on interval and cumulative analyses

One randomized and double-blinded 6-month study in 430 RA patients was conducted in which

an endoscopic examination was performed at 6 months. The results are shown in Figure 3.

Figure 3

Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis



* Significantly different from Celebrex; p<0.001

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials, albeit infrequently (see WARNINGS Gastrointestinal [GI] Effects). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.

Use with Aspirin: Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies 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.

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

INDICATIONS AND USAGE

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation:
Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, 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.

It is unclear, at the present time, how the above rates apply to CELEBREX (see CLINICAL STUDIES-Special Studies). Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically

significant upper GI adverse events in patients taking CELEBREX vs comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. 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 possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

Anaphylactoid reactions were not reported in patients receiving CELEBREX in clinical trials. However**,** as with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No information is available regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

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

Hepatic Effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three 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. In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

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 CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

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 a nonsteroidal anti-inflammatory drug 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 and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-Advanced Renal Disease).

Hematological Effects:

Anemia is sometimes seen in patients receiving CELEBREX. 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. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time

(PTT), and does not appear to inhibit platelet aggregation at indicated dosages (See CLINICAL STUDIES-Special Studies-Platelets).

Fluid Retention and Edema:

Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma:

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

CELEBREX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Risk of Gastrointestinal Ulceration, Bleeding and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

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). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving celecoxib compared with patients on placebo. Other laboratory

abnormalities that occurred more frequently in the patients receiving celecoxib included hypophosphatemia, and elevated BUN. These laboratory abnormalities were also seen in patients who received comparator NSAIDs in these studies. The clinical significance of these abnormalities has not been established.

Drug Interactions

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

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.

Aspirin: CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone (see CLINICAL STUDIES- Special Studies - Gastrointestinal). Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics- Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, caution should be used when administering CELEBREX with warfarin since these patients are at increased risk of bleeding complications.

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 2-4 fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) 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 chromosome 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 BID based on the AUC_{0-24}.

Pregnancy:

Teratogenic effects: Pregnancy Category C. Celecoxib was not teratogenic in rabbits up to an oral dose of 60 mg/kg/day (equal to human exposure at 200 mg BID as measured by AUC_{0-24}); however, at oral doses $\geq$150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), an increased incidence of fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen, was observed. A dose-dependent increase in diaphragmatic hernias was observed in one of two rat studies at oral doses $\geq$30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). There are no studies in pregnant women. CELEBREX 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 dosages $\geq$50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). 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 CELEBREX during the third trimester of pregnancy should be avoided.

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 CELEBREX on labor and delivery in pregnant women are unknown.

Nursing mothers Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the total number of patients who received CELEBREX in clinical trials, more than 2,100 were 65-74 years of age, while approximately 800 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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.

ADVERSE REACTIONS

Of the CELEBREX treated patients in controlled 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 have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have 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.

Adverse events from controlled trials: Table 5 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.

Table 4

Adverse Events Occurring in ≥2% Of Celebrex Patients

	Celebrex (100-200 mg BID) and (200 mg QD)	**Placebo**	**Naproxen** 500 mg BID	**Ibuprofen** 800 mg TID	**Diclofenac** 75 mg BID

	(N=4146)	(N=1864)	(N=1366)	(N=387)	(N=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper resp. tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

	Celebrex (100 - 200 mg BID or 200 mg QD)
Gastrointestinal	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, stomatitis, tooth disorder, vomiting
Cardiovascular	Aggravated hypertension, dry mouth, glaucoma, tenesmus
General	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
Resistance Mechanism Disorders	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
Central, peripheral nervous system	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
Female reproductive	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage,

	vaginitis
Male reproductive	Prostatic disorder
Hearing and vestibular	Deafness, ear abnormality, earache, tinnitus
Heart rate and rhythm	Angina pectoris, coronary artery disorder, myocardial infarction, palpitation, tachycardia
Liver and biliary system	Hepatic function abnormal, SGOT increased, SGPT increased
Metabolic and nutritional	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
Musculoskeletal	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting)	Ecchymosis, epistaxis, thrombocythemia
Psychiatric	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic	Anemia
Respiratory	Bronchitis**,** bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and appendages	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses	Taste perversion
Urinary system	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision	Blurred vision, cataract, conjunctivitis, eye pain

Other serious adverse reactions which occur rarely (<0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients, taking CELEBREX.

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, cholelithiasis, ileus
Hemic and lymphatic:	Thrombocytopenia
Nervous system:	Ataxia

Renal: Acute renal failure

General: Sepsis, sudden death

OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

The lowest dose of CELEBREX should be sought for each patient.

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

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

HOW SUPPLIED

CELEBREX 100-mg capsules are white, 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	**Size**
0025-1520-31	bottle of 100
0025-1520-34	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 **Size**
0025-1525-31 bottle of 100
0025-1525-34 carton of 100 unit dose

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

Rx only **Revised: (date)**

Mfd. for Searle Ltd.
Caguas PR 00725
By Searle & Co.
San Juan PR 00936

Marketed by:
G.D. Searle & Co.
Chicago IL 60680 USA
Pfizer Inc.
New York NY 10017 USA

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Rd.
Skokie IL 60077

 Printed in USA

Searle Pfizer
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(A05264)