PT. Pfizer Indonesia
Local Product Document

Generic Name: Celecoxib
Trade Name: Celebrex
CDS Effective Date: July 20, 2021
Supersedes: November 01, 2019

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. This risk may increase with dose and duration of use. Patients with CV disease or CV risk factors may be at greater risk (see **WARNINGS** and **CLINICAL STUDIES**).

- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk
NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

Asthma and Skin Reaction
CELEBREX is contraindicated to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (see **WARNINGS** and **PRECAUTIONS**).

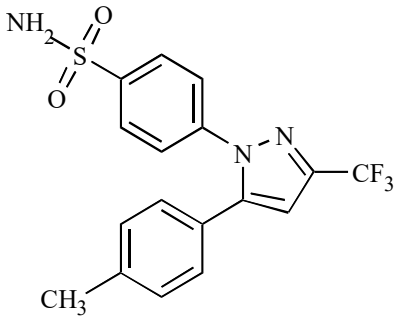
Congestive Heart Failure and Edema
CELEBREX should be used with caution in patients with fluid retention or heart failure (see **WARNINGS**).

Hepatic Effects
Patients with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX (see **PRECAUTIONS**).

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 (see **WARNINGS**).

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 non-steroidal 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. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

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. Because of its lack of platelet effects, CELEBREX is not a substitute for acetyl salicylic acid for CV prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious CV thrombotic adverse events associated with the use of CELEBREX.

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

Pharmacokinetics
Absorption
Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) 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 C_{max} and AUC (see **Food Effects**), which is thought to be due to the low solubility of the drug in aqueous media. 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				
C_{max}, ng/mL	**T_{max}, hour**	**Effective $t_{1/2}$, hour**	**V_{ss}/F, L**	**CL/F, L/hour**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

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

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, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma: a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism.

In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median C_{max} and AUC_{0-24} of celecoxib on day 7 were approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP2C9*3/*3 compared to other genotypes. In three separate single dose studies, involving a total of 5 subjects genotyped as CYP2C9*3/*3, single-dose AUC_{0-24} increased by approximately 3-fold compared to normal metabolizers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% – 1.0% among different ethnic groups.

Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose (see **DOSAGE AND ADMINISTRATION** and **Drug Interactions**).

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.

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%. Co-administration of CELEBREX with an aluminum and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX at doses up to 200 mg BID can be administered without regard to the timing of meals. Higher doses (400 mg BID) 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 C_{max}, T_{max} or $T_{1/2}$ after administration of capsule contents on applesauce.

Special Populations
Geriatric: At steady-state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} 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 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, CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended (see **DOSAGE AND ADMINISTRATION**).

***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, CELEBREX is not recommended in patients with severe renal insufficiency (see **WARNINGS – Advanced Renal Disease**).

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 non-steroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors.

Preclinical Safety Data
Non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity.

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, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily) throughout organogenesis. These effects are expected following inhibition of prostaglandin synthesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival.

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 4200 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 100 mg BID and 200 mg BID provided significant reduction of pain within 24 to 48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the efficacy 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 American College of Rheumatology 20 (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 efficacy and both were comparable to naproxen 500 mg BID.

Although CELEBREX 100 mg BID and 200 mg BID provided similar overall efficacy, 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 to 200 mg BID.

Ankylosing Spondylitis (AS): Celecoxib was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. Celecoxib 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 celecoxib doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to celecoxib 400 mg, 53%, than to celecoxib 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines response 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.

Analgesia: In acute analgesic models of post-oral surgery pain and post-orthopedic surgical pain, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of celecoxib provided pain relief within 60 minutes.

Special Studies

Celecoxib Long-term Arthritis Safety Study (CLASS)
The Celecoxib Long-Term Arthritis Safety Study (CLASS) 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 BID (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg BID (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) acetyl salicylic acid (ASA) for CV 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.

Those patients on CELEBREX and concomitant low-dose ASA (N = 882) experienced 4-fold higher rates of *complicated ulcers* compared to those not on ASA (N = 3105). 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 — Gastrointestinal (GI) Effects**).

The estimated cumulative rates at 9 months of *complicated and symptomatic ulcers* for patients treated with CELEBREX 400 mg BID are described in Table 2. Table 2 also displays results for patients less than or greater than 65 years of age. The difference in rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 2. Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors

	Complicated and Symptomatic Ulcer Rates
All Patients	
Celebrex alone (n = 3105)	0.78
Celebrex with ASA (n = 882)	2.19
Patients <65 Years	
Celebrex alone (n = 2025)	0.47
Celebrex with ASA (n = 403)	1.26
Patients ≥65 Years	
Celebrex alone (n = 1080)	1.40
Celebrex with ASA (n = 479)	3.06

In a small number of patients with a history of ulcer disease, the *complicated and symptomatic ulcer* rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n = 243) and 6.85% (n = 91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see **WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation and ADVERSE REACTIONS – Safety Data from CLASS Study – *Hematological Events***).

Celecoxib versus Omeprazole and Diclofenac for At-risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR) Trial

In this prospective, 24-week study in patients with age ≥60 years or history of gastroduodenal ulcers (users of low-dose aspirin excluded), the percentage of patients with clinically significant GI events (composite primary endpoint) was lower in patients treated with celecoxib 200 mg twice daily compared to patients treated with diclofenac SR 75 mg twice daily plus omeprazole 20 mg once daily. This difference was driven by clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined or presumed GI origin. Results for the individual components of this composite endpoint were as follows:

Predefined Composite GI Endpoint	**Celecoxib 200 mg Twice Daily (N = 2238)**	**Diclofenac SR 75 mg Twice Daily + Omeprazole 20 mg Once Daily (N = 2246)**
Components	**N (%) of Patients**	
Gastroduodenal hemorrhage	3 (0.1)	3 (0.1)
Large bowel hemorrhage	1 (<0.1)	1 (<0.1)
Acute GI hemorrhage of unknown origin	1 (<0.1)	0 (0.0)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined GI origin	5 (0.2)	24 (1.1)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of presumed occult GI origin	10 (0.4)	53 (2.3)
Total*	**20 (0.9)**	**81 (3.6)**

For the following components of the predefined composite GI endpoint, there were no events in either treatment group: gastric outlet obstruction; gastroduodenal, small bowel, or large bowel perforation; small bowel hemorrhage. All events comprising the composite GI endpoint were adjudicated by an independent, expert panel blinded to randomized treatment assignments.
* In a time-to event analysis using life-table techniques, p<0.0001 for the comparison between the celecoxib treatment group and the diclofenac plus omeprazole treatment group for this endpoint.

Cardiovascular Safety

CV safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious CV thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION)

Design

The PRECISION study was a double-blind study of cardiovascular safety in OA or RA patients with or at high risk for cardiovascular disease comparing Celecoxib (200-400 mg daily) with Naproxen (750-1000 mg daily) and Ibuprofen (1800-2400 mg daily). The primary endpoint, Antiplatelet Trialists Collaboration (APTC), was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction or non-fatal stroke. The study was planned with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20-40 mg) for gastro protection. Patients who were taking low-dose Aspirin were permitted to continue therapy.

Other independently adjudicated secondary and tertiary endpoints included cardiovascular, gastrointestinal and renal outcomes. Additionally, there was a 4-month sub study focusing on the effects of the three drugs on blood pressure as measured by ambulatory monitoring (ABPM).

Results

Table 3. Population and Treatment Dose

Analysis Set	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid	Total
Randomized (ITT)	8,072	8,040	7,969	24,081
On-Treatment (mITT)	8,030	7,990	7,933	23,953
Average Dose[1] (mg/day)	209±37	2,045±246	852±103	NA

[1] Average dose dispensed
ITT – Intent to Treat; All randomized subjects
mITT – Modified Intent to Treat: All randomized subjects with at least one dose of study medication and one post baseline visit
bid – Twice a day
tid – Thrice a day
NA –Not Applicable

Primary Endpoint

- Celecoxib, as compared with either naproxen or ibuprofen, met all four prespecified non-inferiority requirements ($p<0.001$ for non-inferiority in both comparisons). Non-inferiority is established when the hazard ratio (HR) ≤1.12 in both ITT and mITT analyses, and upper 95% CI ≤1.33 for ITT analysis and ≤1.40 for mITT analysis.

The primary analysis for ITT and mITT are described below in Table 4.

Table 4. Primary Analysis of the Adjudicated APTC composite endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment through month 43)			
	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.889, 1.40)

Key Secondary and Tertiary Endpoints
The analysis of Major Adverse Cardiovascular Events (MACE)* for mITT are described below in Table 5.

Table 5. On-treatment Adjudicated Major Adverse CV Events

	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
Intent to Treat Analysis (ITT, through month 30)			
N	8,072	8,040	7,969
Subjects with events (%)	377 (4.2%)	384 (4.8%)	346 (4.3%)
Pairwise Comparison	**CELEBREX vs. Naproxen**	**CELEBREX vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
CV-related death[a]	68 (0.8%) vs. 86 (1.1%)	68 (0.8%) vs. 80 (1.0%)	80 (1.0%) vs. 86 (1.1%)
Fatal or non-fatal MI[b]	78 (1.0%) vs. 71 (0.9%)	78 (1.0%) vs. 92 (1.1%)	92 (1.1%) vs. 71 (0.9%)
Fatal or non-fatal stroke[b]	54 (0.7%) vs. 65 (0.8%)	54 (0.7%) vs. 53 (0.7%)	53 (0.7%) vs. 65 (0.8%)
Revascularization[a]	174 (2.2%) vs. 161 (2.0%)	174 (2.2%) vs. 198 (2.5%)	198 (2.5%) vs. 161 (2.0%)
Hospitalization for UA[a]	55 (0.7%) vs. 64 (0.8%)	55 (0.7%) vs. 65 (0.8%)	65 (0.8%) vs. 64 (0.8%)
Hospitalization for TIA[a]	18 (0.2%) vs. 18 (0.2%)	18 (0.2%) vs. 27 (0.3%)	27 (0.3%) vs. 18 (0.2%)
Pairwise Comparison HR (95% CI)	**CELEBREX vs. Naproxen**	**CELEBREX vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
MACE	0.97 (0.83, 1.12)	0.87 (0.75, 1.01)	1.11 (0.69, 1.29)
CV death[a]	0.78 (0.57, 1. 07)	0.84 (.0.61, 1.16)	0.93 (0.69, 1.26)
Fatal or non-fatal MI[b]	1.09 (0.79, 1.50)	0.84 (0.62, 1.14)	1.29 (0.95, 1.76)
Fatal or non-fatal stroke[b]	0.82 (0.57, 1.18)	1.01 (0.69, 1.47)	0.81 (0.56, 1.17)
Revascularization[a]	1.07 (0.87, 1.33)	0.87 (0.71, 1.07)	1.23 (1.00, 1.52)
Hospitalization for UA[a]	0.86 (0.60, 1.23)	0.84 (0.59, 1.21)	1.02 (0.72, 1.44)
Hospitalization for TIA[a]	0.99 (0.51, 1.90)	0.66 (0.37, 1.20)	1.50 (0.83, 2.73)
Modified Intent to Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8,030	7,990	7,933
Number of Subjects with Events (%)			
MACE	247 (3.1%)	284 (3.6%)	253 (3.2%)
CV death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Nonfatal MI	58 (0.7%)	76 (1.0%)	53 (0.7%)
Nonfatal stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)
Hospitalization for unstable angina	46 (0.6%)	49 (0.6%)	44 (0.6%)
Revascularization	132 (1.6%)	158 (2.0%)	122 (1.5%)
Hospitalization for TIA	12 (0.1%)	21 (0.3%)	16 (0.2%)
Pairwise Comparison HR (95% CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
MACE	0.95 (0.80, 1.13)	0.82 (0.69, 0.97)	1.17 (0.98, 1.38)
CV death	0.69 (0.45, 1.07)	0.64 (0.42, 0.99)	1.08 (0.73, 1.60)
Nonfatal MI	1.06 (0.73, 1.54)	0.72 (0.51, 1.01)	1.48 (1.04, 2.11)

Nonfatal stroke	0.93 (0.61, 1.42)	1.26 (0.79, 1.98)	0.74 (0.47, 1.16)
Hospitalization for unstable angina	1.02 (0.67, 1.54)	0.89 (0.59, 1.33)	1.16 (0.77, 1.74)
Revascularization	1.06 (0.83, 1.35)	0.78 (0.62, 0.99)	1.35 (1.07, 1.72)
Hospitalization for TIA	0.73 (0.35, 1.55)	0.54 (0.26, 1.09)	1.38 (0.72, 2.64)

Abbreviations: BD = twice a day; CI = confidence interval; CV - cardiovascular; HR = Hazard ratio; ITT = intent to-treat, MACE = major adverse cardiovascular event; MI = myocardial infarction; mITT = modified intent-to-treat; N = number of subjects in group; TIA = transient ischaemic attack (APTC composite endpoint plus coronary revascularisation, or hospitalisation for unstable angina or transient ischaemic attack); TDS = three times daily; UA = unstable angina.
*MACE = APTC composite endpoint plus coronary revascularization, or hospitalization for unstable angina or transient ischaemic attack.
In the ITT population for the MACE endpoint there were no significant differences, in the pairwise comparisons between treatment regimens.
[a] MACE component endpoints
[b] Overlap of component endpoints = MACE composite endpoints that include fatal/non-fatal outcome (tertiary endpoint).

The analysis of Gastrointestinal Events for ITT and mITT are described below in Table 6.

Table 6. On-treatment Adjudicated Gastrointestinal Endpoints

	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
Intent-to-Treat Analysis (ITT, through month 30)			
N	8,072	8,040	7,969
Subjects with Events, n(%)			
CSGIE	55(0.7%)	72 (0.9%)	56 (0.7%)
IDA of GI Origin	33 (0.4%)	64 (0.8%)	69 (0.9%)
Pairwise Comparison, HR (95% CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
CSGIE	0.97 (0.67, 1.40)	0.76 (0.53, 1.08)	1.27 (0.90, 1,81)
IDA of GI Origin	0.47 (0.31, 0.71)	0.51 (0.33, 0.77)	0.92 (0.65, 1.29)
Modified Intent-to-Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8,030	7,990	7,933
Subjects with Events, n(%)			
CSGIE	27 (0.3%)	59 (0.7%)	52 (0.7%)
IDA of GI Origin	27 (0.3%)	58 (0.7%)	66 (0.8%)
Pairwise Comparison, HR (95% CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
CSGIE	0.51 (0.32, 0.81)	0.43 (0.27, 0.68)	1.16 (0.80, 1.69)
IDA of GI Origin	0.39 (0.25, 0.62)	0.43 (0.27, 0.68)	0.91 (0.64, 1.29)

*CSGIE (Clinically Significant Gastrointestinal Events) = composite of the following; gastroduodenal hemorrhage; gastric outlet obstruction; gastroduodenal, small bowel or large bowel perforation; large bowel hemorrhage; small bowel hemorrhage; Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage; symptomatic gastric or duodenal ulcer.
**IDA (Iron Deficiency Anemia) = clinically significant iron deficiency anemia of GI origin or decrease in Hct (Hematocrit) and/or Hgb (Hemoglobin) (defined as Hct ≥10 points and or Hgb of ≥2 g/dL from baseline.

In the ITT population for the CSGIE endpoint there were no significant differences, in the pairwise comparisons between treatment regimens (data not shown). For the endpoint of iron deficiency anemia of GI origin, significant differences (celecoxib vs. naproxen; celecoxib vs. ibuprofen) and non-significant differences (ibuprofen vs. naproxen) were observed in a manner consistent with the data presented above.

The analysis of clinically significant renal events*, hospitalization for CHF and hypertension for mITT are described below in Table 7.

Table 7. On-treatment Adjudicated Renal Events, Hospitalization for CHF and Hypertension

	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
Intent-to-treat Analysis (ITT, through month 30)			
N	8,072	8,040	7,969
Subjects with first event	118 (1.5%)	166 (2.1%)	139 (7.1%)
Subjects with events, n(%)			
Renal events[a]	57 (0.7%)	92 (1.1%)	71 (0.9%)
Hospitalization for CHF	45 (0.6%)	46 (0.6%)	48 (0.6%)
Hospitalization for hypertension	24 (0.3%)	40 (0.5%)	34 (0.4%)
Pairwise comparison HR (95% CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
Subject with any event	0.83 (0.65, 1.07)	0.70 (0.55, 0.89)	1.19 (0.95, 1.49)
Renal events[a]	0.79 (0.56, 1.12)	0.61 (0.44, 0.85)	1.29 (0.95, 1.76)
Hospitalization for CHF	0.92 (0.61, 1.39)	0.98 (0.65, 1.47)	0.95 (0.63, 1.42)
Hospitalization for hypertension	0.69 (0.41, 1.17)	0.59 (0.36, 0.99)	1.17 (0.74, 1.84)
Modified Intent to Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8,030	7,990	7,933
Subjects with Events, n (%)			
Renal events	42 (0.5%)	73 (0.9%)	62 (0.8%)
Hospitalization for CHF	28 (0.3%)	38 (0.5%)	35 (0.4%)
Hospitalization for hypertension	25 (0.3%)	37 (0.5%)	32 (0.4%)
Any of the Above	89 (1.1%)	139 (1.7%)	120 (1.5%)
Pairwise Comparison, HR (95% CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
Renal events	0.66 (0.44, 0.97)	0.54 (0.37, 0.79)	1.21 (0.86, 1.70)

Table 7. On-treatment Adjudicated Renal Events, Hospitalization for CHF and Hypertension

	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
Hospitalization for CHF	0.77 (0.47, 1.27)	0.70 (0.43, 1.13)	1.12 (0.71, 1.77)
Hospitalization for hypertension	0.76 (0.45, 1.28)	0.64 (0.39, 1.07)	1.18 (0.74, 1.90)
Any of the Above	0.72 (0.55, 0.95)	0.60 (0.46, 0.79)	1.19 (0.93, 1.52)

*N.B: Renal events included a composite of predefined rises in creatinine levels (verified serum creatinine of ≥2.0 mg/dL (177 µmol/L) and an increase of ≥0.7 mg/mL (62 µmol/L)), or hospitalization for acute renal failure (defined as a doubling in serum creatinine, or confirmation of hyperkalemia with ≥50% elevation in serum creatinine), or the initiation of hemodialysis or peritoneal dialysis.

In the ITT population for the endpoint of clinically significant renal events, only the pairwise comparison between celecoxib and ibuprofen was significant, HR 0.61 (0.44, 0.85), no significant differences were observed between treatment regimens in the incidence of hospitalization for congestive heart failure, and a significantly lower incidence of hospitalization for hypertension was observed between celecoxib and ibuprofen, HR 0.59 (0.36, 0.99).

All-cause mortality

In the mITT populations celecoxib, naproxen and ibuprofen were associated with 53 (0.7%), 79 (1.0%), and 73 (0.9%) deaths, respectively. In the ITT population the celecoxib, naproxen and ibuprofen were associated with 132 (1.6%), 163 (2.0%) and 142 (1.8%) deaths, respectively. No significant differences were observed in pairwise comparisons between treatments. All-cause mortality was analyzed as 1 component of the tertiary composite endpoint although it should be noted that the analysis was not adjusted for multiplicity.

ABPM Substudy

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients, at Month 4, celecoxib-treated patients had the smallest change in 24-hour ambulatory systolic blood pressure (SBP) compared to ibuprofen and naproxen: celecoxib produced a slight reduction of 0.3 mmHg while ibuprofen and naproxen increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of -3.9 mmHg (p=0.0009) between celecoxib and ibuprofen; a non-significant difference of -1.8 (p=0.119) mmHg between celecoxib and naproxen, and a non-significant difference of -2.1 mmHg (p=0.0787) between naproxen and ibuprofen.

Cardiovascular Safety – Long-term Studies Involving Patients with Sporadic Adenomatous Polyps

Two studies involving patients with sporadic adenomatous polyps were conducted with celecoxib i.e., the APC trial (Prevention of Sporadic Colorectal Adenomas with Celecoxib) and the PreSAP trial (Prevention of Colorectal Sporadic Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint of CV death, myocardial infarction, or stroke (adjudicated) 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.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of CV death, myocardial infarction, or stroke (adjudicated) 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) and 2.5% (17/685) for 400 mg twice daily and 200 mg twice daily celecoxib treatment groups, respectively, compared with 0.9% (6/679) for placebo group. The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

In the PreSAP trial, the hazard ratios compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily (cumulative rate for this composite endpoint over 3 years was 2.3% [21/933 subjects] compared with 1.9% [12/628 subjects] for placebo).

Cardiovascular Safety – Long-term Study of Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

Data from the ADAPT study did not show a significantly increased CV risk with celecoxib 200 mg twice daily compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 - 2.15) with celecoxib 200 mg twice daily.

Cardiovascular Safety - Meta-analysis from Chronic Usage Studies

A meta-analysis of safety data (adjudicated, investigator-reported serious adverse events) from 39 completed celecoxib clinical studies of up to 65 weeks duration has been conducted, representing 41,077 patients: [23,030 (56.1%) patients exposed to celecoxib 200 mg to 800 mg total daily dose (TDD); 13,990 (34.1%) patients exposed to non-selective NSAIDs; and 4,057 (9.9%) patients exposed to placebo].

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was similar between celecoxib (N = 19,773; 0.96 events/100 patient-years) and non-selective NSAIDs (N = 13,990; 1.12 events/100 patient-years) treatment (RR = 0.90, 95% CI 0.60 - 1.33). This pattern of effect was maintained with or without ASA use (≤325 mg). The adjudicated event rate of non-fatal myocardial infarction trended higher (RR = 1.76, 95% CI 0.93 - 3.35); however, that of non-fatal stroke trended lower (RR = 0.51, 95% CI 0.23 - 1.10), and that of CV death was comparable (RR = 0.57, 95% CI 0.28 - 1.14) for celecoxib compared to combined non-selective NSAIDs.

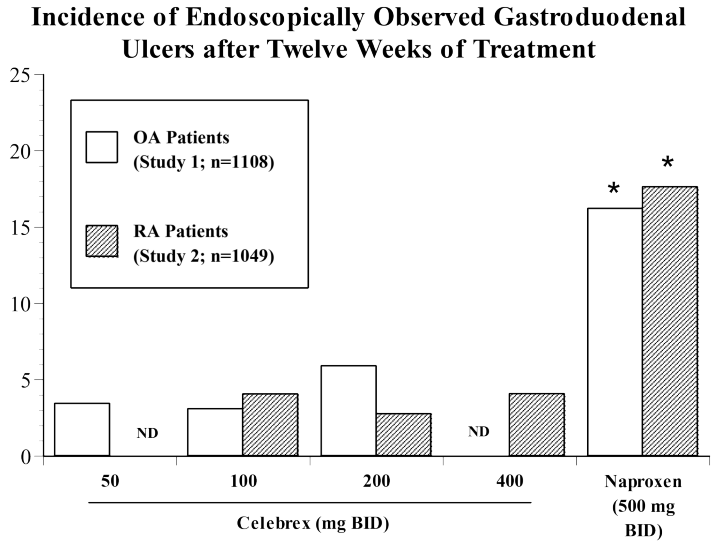
In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was 1.42/100 patient-years for celecoxib (N = 7,462) and 1.20/100 patient-years for placebo (N = 4,057) treatment (RR = 1.11, 95% CI 0.47 - 2.67). This pattern of effect was maintained with or without ASA use (≤325 mg). The incidence of non-fatal myocardial infarction trended higher (RR = 1.56, 95% CI 0.21 - 11.90), as did that of CV death (RR = 1.26, 95% CI 0.33 - 4.77), and that of non-fatal stroke was similar (RR = 0.80, 95% CI 0.19 - 3.31) for celecoxib compared to placebo.

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.

Figure 1 and Table 8 summarize the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcer.

Figure 1



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%

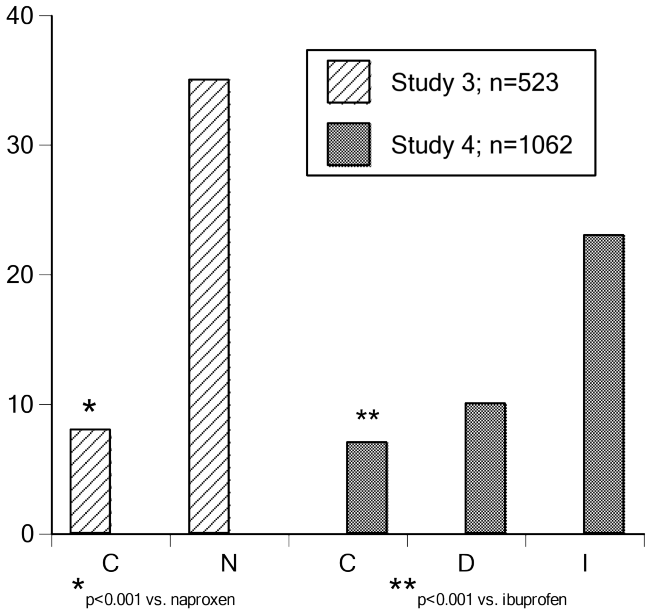
Table 8. Incidence of Gastroduodenal Ulcers from Endoscopic Studies in Osteoarthritis and Rheumatoid Arthritis Patients

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

*p ≤0.05 vs. all other treatments

Figure 2 and Table 8 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

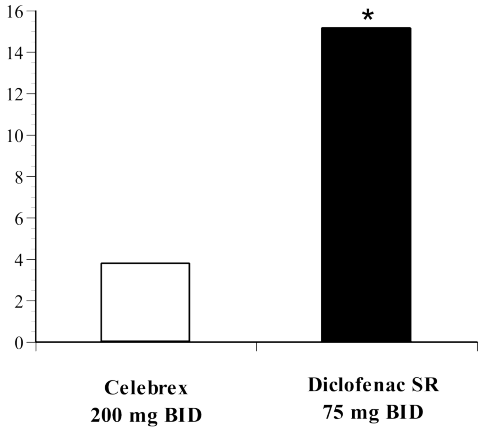
Table 9. Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in Osteoarthritis and Rheumatoid Arthritis Patients

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

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

Gastrointestinal Safety Meta-analysis from Osteoarthritis and Rheumatoid Arthritis Studies
An analysis of 31 randomized controlled clinical studies in OA and RA, involving 39,605 patients with OA (N = 25,903), RA (N = 3,232), or patients with either condition (N = 10,470) compared the incidence of GI adverse events in celecoxib-treated patients to the incidence in patients administered placebo or NSAIDs (including naproxen, diclofenac and ibuprofen). The incidence of clinical ulcers and ulcer bleeds with celecoxib 200 mg to 400 mg total daily dose was 0.2% compared to an incidence of 0.6% with NSAIDs (RR = 0.35; 95% CI 0.22-0.56).

Use with acetyl salicylic acid: Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking acetyl salicylic acid (≤325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in acetyl salicylic acid users than in non-users. However, the increased rate of ulcers in these acetyl salicylic acid users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without *acetyl salicylic acid*.

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**).

CELEBREX is indicated:
1) For relief of the signs and symptoms of osteoarthritis (OA).
2) For relief of the signs and symptoms of rheumatoid arthritis (RA) in adults.
3) For relief of signs and symptoms of ankylosing spondylitis (AS).
4) For the short-treatment of acute pain in adults following surgery or musculoskeletal injury.

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib or any other ingredient of the product.

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 acetyl salicylic acid (ASA [aspirin]) or other NSAIDs, including other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS** - Anaphylactoid Reactions, and **PRECAUTIONS** – Pre-existing Asthma).

CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

Cardiovascular Thrombotic Events
Chronic use of CELEBREX may cause an increased risk of serious adverse CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. In the APC trial, the relative risk for the composite endpoint of CV death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) for the CELEBREX 200 mg twice daily compared to placebo (see **Special Studies – Cardiovascular Safety – Long-term Studies Involving Patients with Adenomatous Polyp Studies**).

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. 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 possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and symptoms of serious CV toxicity and the steps to take if they occur (see **CLINICAL STUDIES**).

There is no consistent evidence that concurrent use of acetyl salicylic acid mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of acetyl salicylic acid and CELEBREX does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal (GI) Effect - Risk of GI Ulceration, Bleeding and Perforation**).

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

Hypertension
As with all NSAIDS, CELEBREX can lead to the onset of new hypertension or worsening of pre-existing 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. Blood pressure should be monitored closely during the initiation of therapy with CELEBREX and throughout the course of therapy (see **Clinical Studies – ABPM Substudy**). 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 **Special Studies - *CLASS***).

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including CELEBREX (see **ADVERSE REACTIONS**). In the CLASS study (see **Special Studies – *CLASS***), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. CELEBREX should be used with caution in patients with fluid retention or heart failure. Celecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation
NSAIDs, including CELEBREX, can cause serious GI events including bleeding, inflammation, ulceration, and upper and lower GI perforation, 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. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA (see **Special Studies - *CLASS***). 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 and who use NSAIDs, have a greater than 10-fold higher 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 CV disease, concomitant use of oral corticosteroids, glucocorticoids, antiplatelet drugs (such as aspirin) or anticoagulants, longer duration of NSAID therapy, 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 in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration. 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. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Use with Other NSAIDs
The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

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 and ACE inhibitors, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib. Discontinuation of NSAID therapy is usually followed

by recovery to the pre-treatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with celecoxib.

Advanced Renal Disease
No information is available regarding the use of CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX is not recommended in these patients with advanced renal disease. If CELEBREX therapy must be initiated, close monitoring of the patient's renal function is advisable (see **DOSAGE AND ADMINISTRATION**).

Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the acetyl salicylic acid 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 acetyl salicylic acid or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS** – Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
CELEBREX is a sulfonamide and can cause serious skin adverse events, such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus (see **PRECAUTIONS** – Pregnancy).

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease 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 non-infectious, 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, including CELEBREX (see **ADVERSE**

REACTIONS – *Post-marketing experience*). In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) 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.

Rare cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis, hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib.

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 PHARMACOLOGY-Special Studies-Platelets**).

Pre-existing Asthma: Patients with asthma may have acetyl salicylic acid-sensitive asthma. The use of acetyl salicylic acid in patients with acetyl salicylic acid-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between acetyl salicylic acid and other non-steroidal anti-inflammatory drugs has been reported in such acetyl salicylic acid - sensitive patients, CELEBREX should not be administered to patients with this form of acetyl salicylic acid sensitivity and should be used with caution in patients with pre-existing asthma.

CYP2D6 Inhibition: Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For drugs that are metabolized by CYP2D6, a dose reduction during initiation of celecoxib treatment or a dose increase upon termination of celecoxib treatment may be necessary (see **Drug Interactions**).

Information for Patients: Patients should be informed of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. CELEBREX, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice if they observe any of these signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS - Cardiovascular Thrombotic Effects**).

2. CELEBREX, like other NSAIDs, can cause gastrointestinal discomfort and, rarely, more serious side effects, such as ulcers and bleeding, which may result in hospitalization and even death. 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 they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS — Gastrointestinal (GI) Effects – Risk of Gastrointestinal Ulceration, Bleeding, and Perforation**).

3. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible. CELEBREX is a sulfonamide and can cause serious skin side effects, such as exfoliative dermatitis, SJS, and TENS, which may result in hospitalizations and even death. These reactions can occur with all NSAIDs, even non-sulfonamides. Although serious skin reactions may occur without

warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity, such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients with prior history of sulfa allergy should not take CELEBREX.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., 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.

6. 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 – Anaphylactoid Reactions**).

7. Patients should be informed that 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.

Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests or renal tests persist or worsen, CELEBREX should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

Drug Interactions

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver.

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended dose (see **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**, Metabolism).

Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

Concomitant administration of celecoxib with inhibitors of CYP2C9 can lead to increases in plasma concentrations of celecoxib. Therefore, a dose reduction of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inhibitors.

Concomitant administration of celecoxib with inducers of CYP2C9, such as rifampicin, carbamazepine and barbiturates can lead to decreases in plasma concentrations of celecoxib. Therefore, a dose increase of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inducers.

Clinical pharmacokinetics study and *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.

Anti-hypertensives including Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II antagonists (also known as angiotensin receptor blockers [ARBs], diuretics and beta-blockers: Inhibition of prostaglandins may diminish the effect of anti-hypertensives including ACEIs, and/or ARBs, diuretics and beta-blockers. This interaction should be given consideration in patients taking celecoxib concomitantly with ACEIs and/or ARBs, diuretics and beta-blockers.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, angiotensin II antagonists or diuretics, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

Results from lisinopril study*:* In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients co-administered with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients co-administered with placebo; this difference was statistically significant.

Cyclosporine*:* Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporine.

Diuretics: 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.

Acetyl salicylic acid: CELEBREX can be used with low dose acetyl salicylic acid. However, concomitant administration of acetyl salicylic acid with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone (see **CLINICAL PHARMACOLOGY — Special Studies — *CLASS*, WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation,** and **WARNINGS – CV Effects**).

Because of its lack of platelet effects, CELEBREX is not a substitute for acetyl salicylic acid for CV prophylaxis.

Fluconazole and ketoconazole: 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 CYP2C9 by fluconazole (see **Pharmacokinetics** - Metabolism). CELEBREX should be introduced at half the recommended dose in patients receiving fluconazole (see **DOSAGE AND ADMINISTRATION**). Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevant inhibition in the metabolism of celecoxib.

Dextromethorphan and metoprolol: Concomitant administration of celecoxib 200 mg twice daily resulted in a 2.6-fold and a 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs as CYP2D6 substrate may need to be reduced when treatment with celecoxib is initiated or increased when treatment with celecoxib is terminated (see **PRECAUTIONS**).

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: No pharmacokinetic and clinically important interactions have been observed in a clinical study between celecoxib and methotrexate.

Use with oral anticoagulants: The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban). Anticoagulation/INR should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin/coumarin-type anticoagulant, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2 mg to 5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Oral contraceptives: In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of a prototype combination oral contraceptive (1 mg norethindrone/0.035 mg ethinyl estradiol).

Other drugs: The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, antacids (aluminum and magnesium), omeprazole, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

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 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}).

Fertility
Based on the mechanism of action, the use of NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including celecoxib, should be considered.

Pregnancy
Teratogenic effects: **Pregnancy Category C. Pregnancy Category D from 30 weeks of gestation onward.**

Risk Summary
Use of NSAIDs, including CELEBREX, during the third semester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

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 ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and 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 ≥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.

Non-teratogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥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.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.

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.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

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. Administration of celecoxib to lactating women has shown very low transfer of celecoxib into breast milk. 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 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 – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation**).

ADVERSE REACTIONS

Clinical Trials Experience

The following adverse drugs reactions (ADRs) in Table 10 were identified with incidence rates greater than 0.01% in celecoxib group and greater than those reported in placebo group, during 12 placebo- and/or active-controlled clinical trials of treatment duration up to 12 weeks at daily doses from 100 mg up to 800 mg in adults.

The frequencies on the ADRs in Table 10 are updated based on a more recent pooling of 89 randomized, controlled clinical trials data representing clinical exposure in 38,102 patients taking celecoxib. ADR frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%). The ADRs in Table 10 are listed by system organ class and ranked by frequency in descending order.

Table 10. Adverse Drug Reactions (ADRs)in 12 placebo- and/or active-controlled clinical trials and ADR frequency from 89 Pain and Inflammation Randomized, Controlled Clinical Trials with Daily Doses of 25 mg to 800 mg, in Adult Populations

System Organ Class Frequency	**Adverse Drug Reaction**
Infections and infestations	
Common	Bronchitis, rhinitis, sinusitis, upper respiratory tract infection, urinary tract infection
Uncommon	Pharyngitis, rhinitis
Blood and lymphatic system disorders	
Uncommon	Anaemia
Rare	Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity
Psychiatric disorders	
Common	Insomnia
Uncommon	Anxiety
Rare	Confusional state
Nervous system disorders	
Common	Dizziness
Uncommon	Hypertonia, somnolence
Eye disorders	
Uncommon	Vision blurred
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Palpitations
Rare	Cardiac failure congestive, arrhythmia, tachycardia
Vascular disorders	
Common	Hypertension (including aggravated hypertension)
Rare	Flushing
Respiratory, thoracic and mediastinal disorders	
Common	Coughing (cough)

Table 10. Adverse Drug Reactions (ADRs)in 12 placebo- and/or active-controlled clinical trials and ADR frequency from 89 Pain and Inflammation Randomized, Controlled Clinical Trials with Daily Doses of 25 mg to 800 mg, in Adult Populations

System Organ Class Frequency	**Adverse Drug Reaction**
Gastrointestinal disorders	
Common	Vomiting, abdominal pain, diarrhoea, dyspepsia, flatulence
Uncommon	Gastric ulcer, tooth disorder
Rare	Duodenal ulcer, oesophageal ulcer
Very rare	Intestinal perforation, pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders	
Common	Pruritus (includes pruritus generalized), rash
Uncommon	Urticaria, ecchymosis
Rare	Angioedema, alopecia
Very rare	Dermatitis bullous
General disorders and administration site conditions	
Common	Oedema peripheral
Uncommon	Face edema, influenza like illness
Injury, poisoning and procedural conditions	
Uncommon	Injury

The following additional adverse drug reactions in Table 11 were identified with incidence rates greater than placebo in long-term polyp prevention studies of duration up to 3 years at daily doses from 400 mg up to 800 mg. (see **CLINICAL STUDIES**, **CV Safety – Long-Term Studies Involving Patients with Sporadic Adenomatous Polyps**)

Frequencies of ADRs in Table 11 were determined based on these long-term polyp prevention studies and defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%). The ADRs in Table 11 are listed by system organ class and ranked by frequency in descending order.

Table 11. Adverse Reactions from Polyp Prevention Studies of Duration up to 3 Years and Daily Doses of 400 mg to 800 mg

System Organ Class Frequency	**Adverse Drug Reaction**
Infections and infestations	
Common	Ear infection, fungal infection**
Uncommon	*Helicobacter* infection, herpes zoster, erysipelas, wound infection, gingivitis, labyrinthitis, bacterial infection
Neoplasms benign, malignant, and unspecified	

Table 11. Adverse Reactions from Polyp Prevention Studies of Duration up to 3 Years and Daily Doses of 400 mg to 800 mg

System Organ Class Frequency	Adverse Drug Reaction
Uncommon	Lipoma
Psychiatric disorders	
Uncommon	Sleep disorder
Nervous system disorders	
Uncommon	Cerebral infarction
Eye disorders	
Uncommon	Vitreous floaters, conjunctival hemorrhage
Ear and labyrinth disorders	
Uncommon	Hypoacusis
Cardiac disorders	
Common	Angina pectoris, myocardial infarction
Uncommon	Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
Vascular disorders	
Very common	Hypertension*
Uncommon	Deep vein thrombosis, haematoma
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Uncommon	Dysphonia
Gastrointestinal disorders	
Very common	Diarrhoea*
Common	Nausea, gastrooesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome
Uncommon	Hemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Hepatobiliary disorders	
Common	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)*
Skin and subcutaneous tissue disorders	
Uncommon	Dermatitis allergic
Musculoskeletal and connective tissue disorders	
Common	Muscle spasms
Uncommon	Synovial cyst
Renal and urinary disorders	
Common	Nephrolithiasis
Uncommon	Nocturia
Reproductive system and breast disorders	
Common	Vaginal haemorrhage, benign prostatic hyperplasia, prostatitis
Uncommon	Breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms

Table 11. Adverse Reactions from Polyp Prevention Studies of Duration up to 3 Years and Daily Doses of 400 mg to 800 mg

System Organ Class Frequency	**Adverse Drug Reaction**
General disorders and administration site conditions	
Uncommon	Oedema
Investigations	
Common	Blood creatinine increased, prostatic specific antigen increased, weight increased
Uncommon	Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
Injury, poisoning and procedural complications	
Uncommon	Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

* Hypertension, vomiting, diarrhoea and hepatic enzyme increased are included in Table 11 because these events were reported more frequently in these studies, which were of 3-year duration, compared to Table 10, which includes adverse reactions from studies of 12-week duration.
** Fungal infections were primarily non-systemic.

Post-marketing Experience
Adverse reactions identified from post-marketing experience are provided below. Even though these were identified as reactions from post-marketing reports, trial data was consulted to estimate frequency. As above, frequencies are based on a pooling of trials representing exposure in 38,102 patients. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), not known (cannot be estimated from the available data).

Immune system disorders: Very rare: anaphylactic reaction.

Psychiatric disorders: Rare: hallucination.

Nervous system disorders: Very rare: cerebral haemorrhage, meningitis aseptic, ageusia, anosmia.

Eye disorders: Uncommon: conjunctivitis.

Vascular disorders: Very rare: vasculitis.

Respiratory, thoracic and mediastinal disorders: Rare: pulmonary embolism, pneumonitis.

Gastrointestinal disorders: Rare: gastrointestinal haemorrhage.

Hepato-biliary disorders: Rare: hepatitis; Very rare: hepatic failure, hepatitis fulminant, hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice.

Skin and subcutaneous tissue disorders: Rare: photosensitivity reaction; Very rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative.

Renal and urinary disorders: Rare: renal failure acute (see **WARNINGS – Renal Effects**), hyponatraemia; Very rare: tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion.

Reproductive system and breast disorders: Rare: menstrual disorder; Not known: infertility female (female fertility decreased).†

General disorders and administration site conditions: Uncommon: chest pain.

† Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable.

Safety Data from CLASS Study:

Hematological Events:
During this study (see **Special Studies – CLASS**), the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) compared to patients on either diclofenac 75 mg BID or ibuprofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with CELEBREX was maintained with or without ASA use (see **CLINICAL PHARMACOLOGY - Platelets**).

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., those causing hospitalization or felt to be life-threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

Adverse events from ankylosing spondylitis studies: A total of 378 patients were treated with CELEBREX in placebo- and active-controlled ankylosing spondylitis studies. Doses up to 400 mg QD were studied. The types of adverse events reported in the ankylosing spondylitis studies were similar to those reported in the arthritis 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.

Adverse events from the controlled trial in familial adenomatous polyposis: The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

OVERDOSAGE

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. 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

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**).

For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient. These doses can be given without regard to timing of meals.

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.

Ankylosing Spondylitis (AS): The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

Management of Acute Pain: The recommended dose 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 maximum 7 days.

Method of Administration
For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature applesauce, rice gruel, yogurt or mashed banana and should be ingested immediately with water. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2°C-8°C/35°F-45°F). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.

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 approximately 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended (see **CLINICAL PHARMACOLOGY – Special Populations**).

CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose (see **Drug Interactions** and **Pharmacokinetics** Metabolism.)

Renal Impairment: There is no clinical experience in patients with severe renal impairment (see **WARNINGS**).

PHARMACEUTICAL PARTICULARS

Incompatibilities
None known.

Special Precautions for Storage
Store below 25°C

Supply
Celebrex 100 mg; carton of 3 blisters @ 10 capsules; Reg. No.: DKL1919809701A1
Celebrex 100 mg; carton of 10 blisters @ 10 capsules; Reg. No.: DKL1919809701A1
Celebrex 200 mg; carton of 3 blisters @ 10 capsules; Reg. No.: DKL2019809701B1
Celebrex 200 mg; carton of 10 blisters @ 10 capsules; Reg. No.: DKL2019809701B1

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Pharmaceuticals LLC, Vega Baja, Puerto Rico

Imported and Packed by:
PT. Pfizer Indonesia
Jakarta, Indonesia

Generic Name: Celecoxib
Trade Name: Celebrex
CDS Effective Date: 1 November 2019
Supersedes: 16 Agustus 2018
Approved by BPOM: 26 Januari 2021

Kapsul CELEBREX®

Celecoxib

Leaflet Kemasan: Informasi bagi pengguna

Isi leaflet ini

Leaflet ini menjawab beberapa pertanyaan umum mengenai Celebrex. Tetapi leaflet tidak memuat semua informasi yang tersedia.

Leaflet ini tidak menggantikan konsultasi dengan dokter atau apoteker Anda.

Semua obat memiliki risiko dan manfaat. Dokter Anda telah mempertimbangkan risiko pemberian Celebrex terhadap manfaat yang diharapkan akan Anda terima.

Jika Anda memiliki kekhawatiran terkait penggunaan obat ini, kemukakan kepada dokter atau apoteker Anda.

Baca leaflet ini dengan cermat sebelum mulai menggunakan Celebrex dan simpan leaflet bersama dengan obat.

Anda mungkin perlu membacanya kembali.

Kegunaan CELEBREX

CELEBREX digunakan untuk:

- meredakan tanda dan gejala osteoartritis
- meredakan tanda dan gejala artritis reumatoid pada orang dewasa
- meredakan tanda dan gejala spondilitis ankilosis
- nyeri akut dengan pengobatan jangka pendek pada orang dewasa setelah pembedahan atau cedera muskuloskeletal

Celebrex termasuk dalam kelompok obat yang disebut Coxib yang digunakan untuk meredakan nyeri dan peradangan dalam beberapa kondisi.

Meskipun Celebrex dapat meredakan gejala nyeri dan peradangan, tetapi tidak akan menyembuhkan kondisi Anda.

Namun demikian, dokter Anda mungkin meresepkan Celebrex untuk tujuan lain.

Tanyakan kepada dokter jika Anda memiliki pertanyaan apa pun mengenai alasan diresepkannya Celebrex kepada Anda.

Keamanan dan efektivitas Celebrex pada pasien anak-anak di bawah usia 18 tahun belum dievaluasi.

Obat ini dapat diperoleh hanya dengan resep dokter.

Sebelum meminum CELEBREX

Kapan Anda dilarang meminumnya

Jangan meminum Celebrex jika:

- **mengalami nyeri perioperatif dalam pembedahan jantung yang disebut *coronary artery bypass graft* (CABG)**

- **pernah mengalami serangan asma, urtikaria, atau reaksi alergi setelah meminum aspirin atau Obat Anti Inflamasi Nonsteroid (AINS, obat yang digunakan untuk mengobati nyeri dan peradangan), termasuk obat-obatan Coxib lainnya**

  Banyak obat yang digunakan untuk mengobati sakit kepala, nyeri haid, dan rasa sakit dan nyeri lainnya yang mengandung aspirin atau AINS.

  Jika Anda alergi terhadap aspirin, AINS, atau obat-obatan Coxib lainnya lalu meminum Celebrex, maka gejala ini dapat bertambah parah.

- **Anda alergi terhadap:**
  - Celebrex
  - bahan apa pun yang tercantum di bagian akhir leaflet ini
  - sulfonamida, kelompok obat yang mencakup, misalnya, antibiotik jenis tertentu (jika Anda tidak yakin apakah Anda meminum salah satu obat ini, tanyakan kepada Apoteker).

Gejala reaksi alergi terhadap obat-obatan ini di antaranya:

- asma, mengi, atau sesak napas
- urtikaria
- pembengkakan wajah atau tenggorokan, kesulitan bernapas, gatal-gatal atau ruam kulit.

Jika Anda alergi terhadap sulfonamida atau salah satu bahan pembuat kapsul lalu Anda meminum Celebrex, maka gejala ini akan bertambah parah.

Tanyakan kepada dokter atau apoteker apakah hal ini berlaku juga pada Anda.

- **jika Anda sudah meminum AINS**
- **jika Anda menderita tukak atau perdarahan lambung**
- **jika Anda menderita penyakit iritasi usus**
- **jika Anda menderita gagal jantung**
- **jika tanggal kedaluwarsa yang tercetak pada kemasan sudah lewat, meskipun kapsul tampak dalam kondisi baik**

  Jika Anda meminum obat ini setelah tanggal kedaluwarsa lewat, obat mungkin tidak akan bekerja dengan baik.
- **jika kemasan sobek atau menunjukkan tanda-tanda kerusakan.**

Jika Anda tidak yakin apakah Anda harus meminum Celebrex, konsultasikan dengan dokter Anda.

Sebelum Anda meminumnya dan secara berkala selama masa terapi

Anda harus memberi tahu dokter jika:

- **menunjukkan tanda dan gejala nyeri dada, sesak napas, lemah, bicara cadel, dan harus meminta saran medis jika mereka mengamati adanya tanda atau gejala ini**
- **menunjukkan tanda dan gejala ulserasi dan perdarahan, dan harus meminta saran medis jika mengamati adanya tanda atau gejala yang merupakan indikasi gangguan ini, di antaranya nyeri epigastrium, dispepsia, melena, dan hematemesis**
- **mengalami ruam kulit dan lepuh dalam bentuk apa pun, demam, atau tanda-tanda hipersensitivitas lainnya seperti gatal-gatal**
- **menunjukkan tanda atau gejala penambahan berat badan yang tidak wajar atau edema**
- **menunjukkan tanda dan gejala hepatoksisitas (misal mual, kelelahan, lemah, pruritus, penyakit kuning, nyeri tekan pada kuadran kanan atas, dan gejala "seperti flu")**
- **menunjukkan tanda dan gejala reaksi anafilaktoid (misal sulit bernapas, pembengkakan wajah, atau tenggorokan)**
- **saat ini menderita diabetes, tekanan darah tinggi, kadar kolesterol tinggi, penyakit kardiovaskuler, faktor risiko kardiovaskuler, gagal jantung, atau memiliki riwayat gangguan jantung atau stroke, atau gangguan sirkulasi pada anggota gerak Anda**

- **dokter telah memberi tahu bahwa Anda menderita penyakit jantung atau pembuluh darah berat yang mempengaruhi sirkulasi darah di otak atau anggota gerak**
- **menderita gangguan hati berat**

  Dokter Anda akan memutuskan apakah kondisi Anda terlalu berat untuk dapat meminum obat ini.
- **menderita gangguan fungsi ginjal**
- **alergi terhadap:**
  - obat-obatan lain
  - zat lain seperti makanan, pewarna, atau bahan pengawet.
- **sedang hamil atau bermaksud untuk hamil**

  Celebrex dapat menyebabkan penutupan duktus arteriosus secara prematur.

  Penggunaan Celebrex tidak disarankan dalam kehamilan kecuali dokter menganggapnya penting.

  Celebrex dapat menyebabkan disfungsi ginjal pada janin yang dapat mengakibatkan penurunan volume cairan amnion atau oligohidramnion dalam kasus yang berat jika digunakan dalam trimester kedua atau ketiga semasa kehamilan.

  Diskusikan hal ini dengan dokter Anda.
- **sedang menyusui atau bermaksud menyusui**

  Sejumlah kecil Celebrex akan masuk ke dalam ASI, oleh karena itu meminum Celebrex selama menyusui harus didiskusikan terlebih dahulu dengan dokter.
- **menderita gangguan kesehatan lainnya seperti:**
  - gangguan hati atau ginjal
  - asma, urtikaria, gatal-gatal, ruam kulit, atau hidung berair
  - tekanan darah tinggi atau retensi cairan
  - tukak lambung (yaitu tukak pada lambung atau usus dua belas jari), memiliki riwayat tukak lambung, atau pernah menderita tukak lambung sebelumnya
  - muntah darah atau materi yang menyerupai ampas kopi
  - perdarahan dari rektum (anus), mengeluarkan feses hitam pekat, atau diare berdarah
- **meminum Celebrex bersama obat apa pun yang digunakan untuk mengobati tekanan darah tinggi dan gangguan jantung lainnya seperti inhibitor ACE, antagonis reseptor angiotensin, penghambat beta, dan diuretik**

  Jika diminum bersama obat-obatan ini dapat menyebabkan gangguan ginjal.
- **meminum alkohol dalam jumlah besar**
- **Anda perokok**
- **saat ini menderita infeksi.**

  Jika Anda diberi Celebrex saat Anda menderita infeksi, maka obat ini dapat menyembunyikan beberapa tanda adanya infeksi.

Jika Anda belum memberi tahu dokter atau apoteker mengenai hal ini, sampaikan hal tersebut sebelum meminum Celebrex.

Meminum obat-obatan lain

Laporkan kepada dokter atau apoteker jika Anda meminum obat-obatan lain, termasuk obat-obatan yang Anda beli tanpa resep dokter dari apotek, supermarket, atau toko obat.

Beberapa obat dan Celebrex dapat saling menghambat. Di antaranya:

- obat apa pun yang digunakan untuk mengobati tekanan darah tinggi dan gangguan jantung lainnya seperti inhibitor ACE, antagonis reseptor angiostensin, penghambat beta, atau diuretik
- flukonazol atau ketonazol, obat antijamur

- litium, obat yang digunakan untuk mengobati beberapa jenis depresi
- warfarin atau obat serupa, obat-obatan yang digunakan untuk menghentikan pembekuan darah
- aspirin atau salisilat, obat-obatan yang digunakan untuk mengobati nyeri
- metotreksat, obat yang digunakan untuk mengobati artritis reumatoid dan beberapa jenis kanker
- obat-obatan tertentu yang digunakan untuk mengobati nyeri dan peradangan yang disebut obat anti inflamasi nonsteroid (AINS) atau (kortiko) steroid
- diuretik, digunakan untuk mengobati hipertensi dan edema.
- rifampisin, karbamazepin, dan barbiturat
- lisinopril
- siklosporin
- dekstrometorfan dan metoprolol
- obat-obatan antiplatelet (seperti aspirin)

Dokter mungkin perlu menyesuaikan dosis obat-obatan ini, atau memberikan saran tambahan jika Anda juga meminum Celebrex.

Cara meminum CELEBREX

Ikuti semua petunjuk yang diberikan dokter atau apoteker kepada Anda dengan cermat.

Petunjuk tersebut mungkin berbeda dengan informasi di dalam leaflet ini.

Jika Anda tidak memahami petunjuk pada label, mintalah bantuan dokter atau apoteker.

Dosis yang harus diminum

Osteoartritis

200 mg satu kali sehari atau 100 mg dua kali sehari.

Artritis reumatoid

100 mg dua kali sehari hingga 200 mg dua kali sehari.

Spondilitis ankilosis

200 mg satu kali sehari atau 100 mg dua kali sehari, beberapa pasien mungkin mendapatkan manfaat dari total dosis harian 400 mg

Penanganan nyeri akut

400 mg sebagai dosis awal diikuti dengan 200 mg, jika diperlukan pada hari pertama. Pada hari berikutnya, dosis yang disarankan adalah 200 mg dua kali sehari maksimum 7 hari.

Cara meminum

Telan seluruh kapsul dengan segelas cairan. Anda dapat meminum Celebrex sebelum atau sesudah makan.

Durasi meminum obat

Bergantung kondisi, Anda mungkin perlu meminum Celebrex selama beberapa hari atau selama periode yang lebih panjang. Khusus untuk nyeri akut, Anda mungkin perlu meminum Celebrex hingga maksimum 7 hari.

Celebrex tidak akan menyembuhkan kondisi Anda tetapi dapat membantu mengendalikan rasa sakit, pembengkakan, dan kekakuan.

Gunakan Celebrex sesuai anjuran dokter.

Jangan melebihi dosis yang disarankan oleh dokter.

Jika Anda lupa meminum obat

Jika sudah hampir mencapai waktu untuk meminum dosis berikutnya, lompati dosis yang terlewat dan minumlah dosis berikut yang diharuskan. Jika tidak, minumlah segera setelah Anda ingat, kemudian lanjutkan meminum kapsul Anda seperti biasanya.

Jangan meminum dosis ganda untuk mengejar dosis yang terlewat.

Jika Anda meminum obat terlalu banyak (overdosis)

Segera hubungi dokter untuk meminta saran, atau datanglah ke Unit Gawat Darurat di rumah sakit terdekat di wilayah Anda jika merasa bahwa diri Anda atau orang lain telah meminum terlalu banyak Celebrex. Lakukan hal ini sekali pun tidak ada tanda-tanda ketidaknyamanan atau keracunan. Anda mungkin memerlukan penanganan medis segera.

Jika meminum terlalu banyak Celebrex, Anda mungkin merasa lelah, mengantuk, mual, muntah, dan sakit perut. Anda mungkin juga mengalami kesulitan bernapas dan merasa ingin pingsan.

Selama meminum obat

Yang harus Anda lakukan

Jika Anda hamil saat meminum Celebrex, sampaikan segera ke dokter Anda.

Jika Anda akan memulai obat baru apa pun, sampaikan kepada dokter atau apoteker bahwa Anda sedang meminum Celebrex.

Sampaikan kepada semua dokter, dokter gigi, dan apoteker yang merawat Anda bahwa Anda sedang meminum Celebrex.

Jika Anda mengalami ruam kulit (misal urtikaria, bintik-bintik) saat diobati dengan Celebrex, segera hubungi dokter.

Munculnya gangguan ini, jika terjadi, dapat terjadi kapan saja, tetapi paling sering terjadi dalam bulan pertama pengobatan.

Yang tidak boleh Anda lakukan

Jangan berikan Celebrex kepada siapa pun, sekali pun mereka mengalami gejala atau kondisi yang sama seperti Anda.

Jangan meminum Celebrex untuk mengobati keluhan lain kecuali diperintahkan oleh dokter Anda.

Efek samping

Periksakan ke dokter segera setelah Anda mengalami gangguan apa pun selama meminum Celebrex, sekali pun Anda tidak merasa bahwa gangguan tersebut terkait dengan obat ini atau tidak tercantum dalam leaflet ini.

Seperti obat-obatan lain, Celebrex dapat menimbulkan sejumlah efek samping. Jika terjadi efek samping maka kemungkinan sifatnya ringan dan sementara.

Jika Anda memiliki pertanyaan apa pun, tanyakan kepada dokter atau apoteker.

Beri tahu dokter jika Anda mengamati adanya berikut ini:

- alergi yang bertambah parah
- batuk
- sakit perut, diare, dispepsia, kembung

- pruritus, ruam
- gejala seperti flu, edema perifer
- cedera
- infeksi telinga, infeksi jamur
- *angina pectoris*, infark miokardium
- hipertensi
- dispnea
- spasme otot
- nefrolitiasis
- hiperplasia prostat jinak, prostatitis
- peningkatan kreatinin darah, peningkatan antigen spesifik prostatik, penambahan berat badan yang tidak wajar
- pusing, hipertonia
- bronkitis, faringitis, rinitis, sinusitis, infeksi saluran pernapasan atas
- infeksi saluran kencing
- insomnia
- gangguan gigi.

Beri tahu dokter segera jika Anda mengamati salah satu yang berikut ini:

- reaksi kulit yang serius seperti sindrom reaksi obat dengan eosinofilia dan gejala sistemik (DRESS), dermatitis eksfoliatif, sindrom Stevens-Johnson, dan nekrolisis epidermal toksik
- tanda dan gejala nyeri dada, sesak napas, lemah, bicara cadel
- tanda dan gejala ulserasi dan perdarahan
- ruam kulit dan bisul, demam, atau tanda hipersensitivitas lainnya seperti gatal-gatal
- menunjukkan tanda atau gejala penambahan berat badan yang tidak wajar atau edema
- tanda dan gejala hepatoksisitas (misal mual, kelelahan, lemah, pruritus, penyakit kuning, nyeri tekan pada kuadran kanan atas, dan gejala “seperti flu”)
- tanda dan gejala reaksi anafilaktoid (misal kesulitan bernapas, pembengkakan wajah atau tenggorokan)

Ini semua merupakan efek samping serius. Anda mungkin memerlukan penanganan medis segera.

Tidak semua efek samping dengan Celebrex telah dilaporkan tetapi diamati pada obat-obatan sejenis.

Efek samping lain yang tidak tercantum di atas mungkin dialami oleh beberapa orang.

Jangan terlalu khawatir dengan daftar kemungkinan efek samping ini.

Anda mungkin tidak akan mengalaminya.

Sampaikan dokter jika mengamati hal-hal lain yang membuat Anda merasa kurang nyaman, sekali pun tidak tercantum di dalam daftar.

Setelah meminum CELEBREX

Penyimpanan

Simpan di bawah suhu 25°C

HARUS DENGAN RESEP DOKTER

Pembuangan

Jika dokter memberi tahu Anda untuk menghentikan Celebrex, atau kapsul telah melewati tanggal kedaluwarsa, tanyakan kepada apoteker mengenai tindakan yang harus dilakukan terhadap sisa obat.

Deskripsi produk

Bentuknya

- Celebrex 100 mg – Kapsul gelatin keras berwarna putih legap dengan tinta biru bertuliskan “100” warna putih. Kapsul putih legap dengan tinta biru bertuliskan “7767” warna putih.

  Kapsul 100 mg dikemas dalam karton berisi 3 blister @ 10 kapsul; No. Reg.: DKL1919809701A1.

  Kapsul 100 mg dikemas dalam karton berisi 10 blister @ 10 kapsul; No. Reg.: DKL1919809701A1.
- Celebrex 200 mg – Kapsul gelatin keras berwarna putih legap dengan tinta emas bertuliskan “200” warna putih. Kapsul putih legap dengan tinta emas bertuliskan “7767” warna putih.

  Kapsul 200 mg dikemas dalam karton berisi 3 blister @ 10 kapsul No. Reg.: DKL2019809701B1.

  Kapsul 200 mg dikemas dalam karton berisi 10 blister @ 10 kapsul No. Reg.: DKL2019809701B1.

Kandungan bahan

Bahan aktif

Bahan aktif dalam Celebrex adalah celecoxib.

- Celebrex 100 mg - 100 mg celecoxib/kapsul
- Celebrex 200 mg - 200 mg celecoxib/kapsul

Zat tambahan

- laktosa monohidrat
- natrium lauril sulfat
- povidonem K30
- natrium croscarmellose
- magnesium stearat
- air demineralisasi

Celebrex tidak mengandung sukrosa, gluten, tartrazin atau pewarna azo lainnya.

Diimpor dan Dikemas oleh:

PT. Pfizer Indonesia
Jakarta, Indonesia

Produsen:

Pfizer Pharmaceuticals LLC
Vega Baja,
Puerto Rico