COXIB-200
CELECOXIB CAPSULES 200 mg

PRODUCT NAME
COXIB, Celecoxib capsules 200 mg

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S):
Celecoxib 200 mg

PRODUCT DESCRIPTION:
White opaque/White opaque, size '1' hard gelatin capsule printed with 'M' on cap and 13 on the body, filled with white to off white granular powder

List of Excipients:
Lactose Monohydrate, Croscarmellose Sodium, Povidone K-30, Sodium lauryl Sulfate, Croscarmellose Sodium, Magnesium stearate, Gelatin, Titanium Dioxide, Black Iron Oxide, Butyl Alcohol, Dehydrated Alcohol, Isopropyl Alcohol, Potassium Hydroxide, Shellac, Strong Ammonia Solution

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
Pharmacotherapeutic Group: Coxibs. ATC Code: M01AH.
Pharmacology: Pharmacodynamics: Mechanism of Action: The mechanism of action of celecoxib is via inhibition of prostaglandin synthesis primarily by inhibition of cyclooxygenase 2 (COX-2). At therapeutic concentrations in humans celecoxib does not inhibit cyclooxygenase 1 (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoid, in particular prostaglandin E2, causing inflammation, edema and pain. Celecoxib acts as an anti-inflammatory, analgesic, and antipyretic agent in animal models by blocking the production of inflammatory prostanoid via COX-2 inhibition. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.
In vivo and ex vivo studies show that celecoxib has a very low affinity for the constitutively expressed COX-1 enzyme. Consequently at therapeutic doses celecoxib has no effect on prostanoid synthesized by activation of COX-1 thereby not interfering with normal COX-1 related physiological processes in tissues, particularly the stomach, intestine, and platelets.
Clinical Studies
Osteoarthritis (OA): Celecoxib has demonstrated significant reduction in joint pain compared to placebo. Celecoxib was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with celecoxib 100 mg twice daily or 200 mg once daily 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, celecoxib doses of 100 mg twice daily or 200 mg twice daily provided significant reduction of pain within 24 to 48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the efficacy of celecoxib was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.
Rheumatoid Arthritis (RA): Celecoxib has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib 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. Celecoxib 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. Celecoxib doses of 100 mg twice daily and 200 mg twice daily were similar in efficacy and both were comparable to naproxen 500 mg twice daily.
Although celecoxib 100 mg twice daily and 200 mg twice daily provided similar overall efficacy, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100 mg to 200 mg twice daily.
Analgesia, including Primary Dysmenorrhea: In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of celecoxib provided pain relief within 60 minutes.
Ankylosing Spondylitis (AS): Celecoxib was evaluated in AS patients in two placebo- and active-controlled (naproxen or ketoprofen) 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 Assessment of Disease, Patient's Global Pain Intensity, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.
Chronic Low Back Pain (LBP): Celecoxib was used to treat patients who had pre-existing non-neuropathic LBP of duration ≥12 weeks. In the table shown below, efficacy results in 5 clinical trials of up to 12 weeks duration are presented using the Patient's Assessment of Pain Intensity (100 mm visual analog scale) from baseline to end of treatment:

Patient's Assessment of Pain Intensity in LBP Clinical Trials Study ID (Duration) Treatment (TDD)	**N**	**Baseline Pain Intensity**	**Change in Pain Intensity**	**P-Value for Treatment Difference**
Study 244 (12 Weeks)a				

Placebo	177	76.6	-30.1	--
Celecoxib 200 mg	183	73.6	-35.9	0.0503
Study 245 (12 Weeks)a				
Placebo	191	75.7	-26.2	--
Celecoxib 200 mg	183	72.8	-32.2	0.0427
Study 1165 (6 Weeks)b				
Celecoxib 400 mg	402	65.5	-34.6	0.008
Tramadol 200 mg	389	66.1	-30.4	--
Study 1338 (6 Weeks)b				
Celecoxib 400 mg	386	65.9	-34.8	0.595
Tramadol 200 mg	385	66.6	-34.4	--
Study 1174 (4 Weeks)				
Placebo	410	65.1	-26.2	--
Celecoxib 400 mg	410	65.0	-31.7	<0.001
Loxoprofen 180 mg	407	65.6	-29.3	Not Evaluated

N = Number of patients providing data at baseline and end of treatment. TDD = Total daily dose.
a Patient's Assessment of Pain Intensity a co-primary efficacy measure in these studies, along with Patient's Global Assessment of Low Back Pain (treatment differences significantly favored celecoxib over placebo in Studies 244 and 245) and the Roland-Morris Disability Questionnaire (treatment difference significantly favoured celecoxib over placebo in Study 244).
b The primary efficacy measure in these studies was the percentage of patients who experienced at least 30% improvement on the Numerical Rating Scale (NRS) Pain Assessment, for which results in both studies showed statistical superiority for celecoxib over tramadol.
c Based on least-squares means from Analysis of Covariance models, with changes in pain intensity calculated by subtracting baseline value from end-of-treatment value; p-values were calculated based on least-squares mean differences between treatment groups.

Pharmacokinetics:
Absorption: The pharmacokinetics of celecoxib has been evaluated in approximately 1500 individuals. When given under fasting conditions celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Oral bioavailability from capsules is about 99% relative to administration in suspension (optimally available oral dosage form). Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg twice daily; at higher doses there are less than proportional increases in C_{max} and AUC.
Distribution: Plasma protein binding, which is concentration independent, is about 97% at therapeutic plasma concentrations and celecoxib is not preferentially bound to erythrocytes in the blood.
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 & Administration and Interactions).
Excretion: Elimination of celecoxib is mostly by hepatic metabolism with less than 1% of the dose excreted unchanged in urine. After multiple dosing, elimination half-life is 8-12 hours and the rate of clearance is about 500 mL/min. With multiple dosing steady-state plasma concentrations are reached before Day 5. The intersubject variability on the main pharmacokinetic parameters (AUC, C_{max}, elimination half-life) is about 30%. The mean steady-state volume of distribution is about 500 L/70 kg in young healthy adults indicating wide distribution of celecoxib into the tissues. Preclinical studies indicate that the drug crosses the blood/brain barrier.
Food Effects: Dosing with food (high fat meal) delays absorption of celecoxib resulting in a T_{max} of about 4 hours and increases bioavailability by about 20% (see Dosage & Administration).
Special Populations: Elderly: In the population >65 years, there is a one and a half to two-fold increase in mean C_{max} and AUC for celecoxib. This is a predominantly weight-related rather than age-related change, celecoxib levels being higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Therefore, elderly females tend to have higher drug plasma concentrations than elderly males. No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), initiate therapy at the lowest recommended dose
Race: A meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in the Black population compared to Caucasians. The cause and clinical significance of this finding is unknown.
Hepatic impairment: Plasma concentrations of celecoxib in patients with mild hepatic impairment (Child-Pugh Class A) are not significantly different from those of age and sex matched controls. In patients with moderate hepatic impairment (Child-Pugh Class B) celecoxib plasma concentrations are about twice those of matched controls (see Dosage & Administration).
Renal impairment: In elderly volunteers with age-related reductions in glomerular filtration rate (GFR) (mean GFR>65 mL/min/1.73 m^2) and in patients with chronic stable renal insufficiency (GFR 35-60 mL/min/1.73 m^2) celecoxib pharmacokinetics was comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. Severe renal insufficiency would not be expected to alter clearance of celecoxib since the main route of elimination is via hepatic metabolism to inactive metabolites.

Renal effects: The relative roles of COX-1 and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\infty}$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown celecoxib produces no decreases in GFR in the elderly or those with chronic renal insufficiency. These studies have also shown transient reductions in fractional excretion of sodium. In studies in patients with arthritis a comparable incidence of peripheral edema has been observed to that seen with non-specific COX-inhibitors (which also possess COX-2 inhibitory activity). This was most evident in patients receiving concomitant diuretic therapy. However increased incidences of hypertension and cardiac failure have not been observed and the peripheral edema has been mild and self-limiting.

INDICATIONS:

- Symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).
- Relief of signs and symptoms of ankylosing spondylitis (AS).
- Management of acute pain.
- Treatment of primary dysmenorrhea.
- Management of low back pain.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see Sections Contraindications and Special warnings and precautions for use), taking into consideration other available therapeutic options.

RECOMMENDED DOSAGE:

Celecoxib capsules, at doses up to 200 mg twice per day, can be taken with or without food.
As the cardiovascular (CV) risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.
***Symptomatic Treatment of Osteoarthritis (OA)*:** The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day.
***Symptomatic Relief in the Treatment of Rheumatoid Arthritis (RA)*:** The recommended daily dose of celecoxib is 100 mg or 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.
The maximum recommended daily dose is 400 mg for above indications.
***Management of Acute Pain in Adults*:** The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.
Management of Chronic Low Back Pain in Adults: The recommended dose of celecoxib is 200 or 400 mg daily, administered as a 200 mg single dose, or as 100 or 200 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.
***Treatment of Primary Dysmenorrhea*:** The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.
***Elderly*:** No dosage adjustment is generally necessary. However, for elderly patients weighing less than 50 kg, it is advisable to initiate therapy at the lowest recommended dose.
Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib

MODE/ROUTE 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 (2-8°C). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.
Hepatic Impairment: No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Treatment should be initiated at half the recommended dose in patients with moderate hepatic impairment (with serum albumin 25-35 g/L or Child-Pugh Class B).
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied (see Special warnings and precautions for use – Hepatic Effects). The use of celecoxib in this patient population is not recommended.
***Renal Impairment*:** No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment. The use of celecoxib in this patient population is not recommended.
Co-administration with Fluconazole: Celecoxib should be introduced at half the recommended dose in patients receiving fluconazole, a CYP2C9 inhibitor. Caution is advised when co-administering celecoxib with other CYP2C9 inhibitors.
Pediatric Patients: Celecoxib has not been studied in subjects under 18 years of age.
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.

CONTRAINDICATIONS:

Celecoxib is contraindicated in:
Patients with known hypersensitivity to celecoxib or any other ingredient of the product
Patients with known sulfonamide hypersensitivity
Patients with active peptic ulceration or gastrointestinal (GI) bleeding
Patients who have experienced asthma, urticaria or allergic-type reactions after taking acetylsalicylic acid (ASA [aspirin]) or other non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Section Special warnings and precautions for use)
Congestive heart failure (NYHA II-IV)
Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease

WARNING AND PRECAUTIONS:

Cardiovascular Effects: Cardiovascular Thrombotic Events: Celecoxib may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs 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 celecoxib, 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 Pharmacology: Pharmacodynamics under Actions).
Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see Contraindications).
Celecoxib is not a substitute for aspirin for prophylaxis of CV thromboembolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, anti-platelet therapies (e.g., aspirin) should not be discontinued.
Hypertension: As with all NSAIDs, celecoxib 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. NSAIDs, including celecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy (see Pharmacology: Pharmacodynamics: Clinical Studies under Actions).
Fluid Retention and Edema: As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking celecoxib. Therefore, patients with pre-existing congestive heart failure (CHF) or hypertension should be closely monitored. 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: Upper and lower GI perforations, ulcers or bleeds have occurred in patients treated with celecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant aspirin, glucocorticoids, or other NSAIDs, patients using alcohol or patients with a prior history of, or active, GI disease, such as ulceration, GI bleeding or inflammatory conditions. Most spontaneous reports of fatal GI events have been in elderly or debilitated patients.
Renal Effects: NSAIDs including celecoxib may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.
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: Renal function should be closely monitored in patients with advanced renal disease who are administered celecoxib (see Dosage & Administration).
Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib (see Contraindications).
Serious Skin Reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. 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. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Hepatic Effects: Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of celecoxib in patients with severe hepatic impairment is not recommended. Celecoxib should be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class B), and initiated at half the recommended dose (see Dosage & Administration).
Rare cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis, and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib.
A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib.
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). In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant after initiating treatment with celecoxib or changing the dose (see Interactions).
General: By reducing inflammation, celecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections.
The concomitant use of celecoxib and non-aspirin NSAID should be avoided.
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 Interactions).
Effects on Ability to Drive and Use Machines: The effect of celecoxib on ability to drive or use machinery has not been studied, but based on its Pharmacodynamic properties and overall safety profile it is unlikely to have an effect.

INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION:
General: Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 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 & Administration and Pharmacology: Pharmacokinetics under Actions).
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 CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.
Drug-specific: *Interaction of celecoxib with warfarin or similar agents:* See Use with Oral Anticoagulants under Precautions.
Lithium: In healthy subjects, lithium plasma levels increased approximately 17% in subjects receiving lithium together with celecoxib. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.
Aspirin: Celecoxib does not interfere with the anti-platelet effect of low-dose aspirin (see Gastrointestinal (GI) Effects under Precautions). Because of its lack of platelet effects, celecoxib is not a replacement for aspirin in the prophylactic treatment of CV disease.
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.
Fluconazole and ketoconazole: Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via CYPP450 2C9 by fluconazole. Celecoxib should be introduced at half the recommended dose in patients receiving the CYP2C9 inhibitor fluconazole (see Dosage & 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 CYP2D6 Inhibition under Precautions).
Diuretics: Clinical studies have shown that NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.
Methotrexate: No pharmacokinetic and clinically important interactions have been observed in a clinical study between celecoxib and methotrexate.
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: No clinically important interactions have been observed with celecoxib and antacids (aluminum and magnesium), omeprazole, glibenclamide (glyburide), phenytoin, or tolbutamide.

PREGNANCY AND LACTATION:
Impairment of Fertility: Based on the mechanism of action, the use of NSAIDs, including celecoxib, 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.
Use in Pregnancy: There are no studies in pregnant women. Studies in animals have shown reproductive toxicity (see Pharmacology: Pharmacodynamics: Toxicology under Actions). The relevance of these data for humans is unknown.
Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during the third trimester of pregnancy.
Celecoxib should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
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.
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. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.
Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.
Use in Lactation: Studies in rats show that celecoxib is excreted in milk at concentrations similar to those in plasma. Administration of celecoxib to lactating women has shown very low transfer of celecoxib into breast milk. Because of the potential for adverse reactions in nursing infants from celecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS:
Clinical Trials Experience: The following adverse drug reactions (ADRs) in Table 11 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 11 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 11 are listed by system organ class and ranked by frequency in descending order.
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 -800 mg, in Adult Populations.

System Organ Class Frequency	Adverse Drug Reaction
Infections and infestations Common Uncommon	Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection Pharyngitis, rhinitis

Blood and lymphatic system disorders Uncommon Rare	Anemia Thrombocytopenia
Immune system disorders	Hypersensitivity

Uncommon	
Psychiatric disorders Common Uncommon Rare	Insomnia Anxiety Confusional state
Nervous system disorders Common Uncommon	Dizziness Hypertonia, Somnolence
Eye disorders Uncommon	Vision blurred
Ear and labyrinth disorders Uncommon	Tinnitus
Cardiac disorders Uncommon Rare Cardiac	Palpitation failure congestive, arrhythmia, tachycardia
Vascular disorders Common Rare	Hypertension (including aggravated hypertension) Flushing
Respiratory, thoracic and mediastinal disorders Common	Cough
Gastrointestinal disorders Common Uncommon Rare Very rare	Vomiting, abdominal pain, diarrhoea, dyspepsia, flatulence Gastric ulcer, tooth disorder Duodenal ulcer, oesophageal ulcer Intestinal perforation, pancreatitis
Hepatobiliary disorders Uncommon	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders Common Uncommon Rare Very rare	Pruritus (includes pruritus generalized), rash Urticaria, ecchymosis Angioedema, alopecia Dermatitis bullous
General disorders and administration site conditions Common Uncommon	Oedema peripheral Face oedema, influenza like illness
Injury, Poisoning and Procedural Conditions Uncommon	Injury

The following additional adverse drug reactions in Table 12 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 Pharmacology: Pharmacodynamics under Actions). Frequencies of ADRs in Table 12 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 12 are listed by system organ class and ranked by frequency in descending order.

System Organ Class Frequency	Adverse Drug Reaction
Common Uncommon	Ear infection, fungal infection ** Helicobacter infection, herpes zoster, erysipelas, wound infection, gingivitis, labyrinthitis, bacterial infection
Neoplasms benign, malignant, and unspecified Uncommon	Lipoma
Psychiatric disorders Uncommon	Sleep disorder

Nervous system disorders Uncommon	Cerebral infarction
Eye disorders Uncommon	Conjunctival hemorrhage, vitreous floaters
Ear and labyrinth disorders	Hypoacusis

Uncommon	
Cardiac disorders Common Uncommon	Myocardial infarction, angina pectoris Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
Vascular disorders Very Common Uncommon	Hypertension* Deep vein thrombosis, haematoma
Respiratory, thoracic, and mediastinal disorders Common Uncommon	Dyspnoea Dysphonia
Gastrointestinal disorders Very Common Common Uncommon	Diarrhoea* Vomiting*, dysphagia, irritable bowel syndrome, gastroesophageal reflux disease, nausea, diverticulum Haemorrhoidal 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 Uncommon	Muscle spasms Synovial cyst
Renal and urinary disorders Common Uncommon	Nephrolithiasis Nocturia
Reproductive system and breast disorders Common Uncommon	Vaginal haemorrhage, prostatitis, benign prostatic hyperplasia Ovarian cyst, menopausal symptoms, breast tenderness, dysmenorrhea
General disorders and administration site conditions Uncommon	Oedema
Investigations Common Uncommon	Blood creatinine increased, prostatic specific antigen increased, weight increased Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
Injury, poisoning and procedural complications Uncommon	Foot fracture, lower limb fracture, fracture, epicondylitis, tendon rupture

*Hypertension, vomiting, diarrhoea, and hepatic enzyme increased are included in Table 12 because these events were reported more frequently in these studies, which were of 3-year duration, 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 as follows. Even though these were identified as reactions from post-marketing reports, trial data was consulted to estimate frequency. As previously mentioned, 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, and 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 (see Hepatic Effects under Precautions), 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 generalized exanthematous pustulosis (AGEP), dermatitis exfoliative.
Renal and urinary disorders: Rare: Renal failure acute (see Renal Effects under Precautions), 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) (see Use in Pregnancy & Lactation).†
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.

OVERDOSE AND TREATMENT:
Clinical experience of overdose is limited. Single doses up to 1,200 mg and multiple doses up to 1,200 mg twice daily have been administered to healthy subjects without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided. Dialysis is unlikely to be an efficient method of drug removal because of high protein-binding of the drug.

STORAGE:
Store below or at 30°C. Keep away from the reach of children.

DOSAGE FORMS OR PRESENTATION:
Capsules
Alu-Clear PVC/ PVDC blister packs of 10 capsules

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