210X260MM front & back printing

For the use only of a registered Medical Practitioner or a Hospital or a Laboratory

GELOXIB-200
(Celecoxib Capsules 200 mg)

COMPOSITION:
Each capsule contains:
Celecoxib BP 200 mg

DESCRIPTION:
Geloxib-200 is Dark Green/Dark Green coloured hard gelatin capsule shell of size "2", containing white granular powder.

PHARMACODYNAMICS / PHARMACOKINETICS:
Pharmacodynamic Effects:
Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductusarteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.
The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.
Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide antibiotics).
A dose dependent effect on TxB2 formation has been observed after high doses of celecoxib. However, in healthy subjects, in small multiple dose studies with 600 mg BID (three times the highest recommended dose) celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.
Pharmacokinetic properties:
Absorption
Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption of celecoxib by about 1 hour resulting in a T_{max} of about 4 hours and increases bioavailability by about 20%.
Distribution
Plasma protein binding, which is concentration independent, is about 97% at therapeutic plasma concentrations and the drug 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.
Cytochrorne 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.
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.
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 500L/70 kg in young healthy adults indicating wide distribution of celecoxib into tissues. Pre-clinical 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%.
Special Populations
Elderly
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.
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 6) celecoxib plasma concentrations are about twice those of matched controls.
Renal impairment: 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-$PGF_{1\alpha}$ (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:
For the management of acute pain in adults and for the treatment of primary dysmenorrhoea.
Relief of the acute and chronic pain and inflammation of rheumatoid arthritis and osteoarthritis.
Relief of signs and symptoms of ankylosing spondylitis.
For the management of low back pain.

DOSE AND ADMINISTRATION:
Celecoxib capsules can be taken with or without food.
Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.
Adults
Symptomatic Treatment of Osteoarthritis (OA): Therecommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day.
Symptomatic Treatment of Rheumatoid Arthritis (RA): The recommended 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 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.
Management of Acute Pain: 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.
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.
Low Back Pain (LBP): Usual dosage for adults is 100 mg of celecoxib orally twice daily, morning and evening after meal, or 200 mg once daily (100 mg and 200 mg only).
Elderly: No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), it is advisable to initiate therapy at the lowest recommended dose.
Hepatic impairment: No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Introduce celecoxib at half the recommended dose in arthritis or pain patients with moderate hepatic impairment (Child-Pugh Class B).
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied **(see Warning and Precaution- Hepatic Effects)**
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.
Children: Celecoxib is not indicated for use in Children **(see Warning and Precaution- Renal Effects)**
CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the close to half the lowest recommended dose **(see Pharmacokinetic properties-Metabolism).**

CONTRAINDICATIONS:
Celecoxib is contraindicated in patients with known hypersensitivity to celecoxib.
Celecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.
Celecoxib is contraindicated for patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke).
Celecoxib should not be given to patients who have experiences asthma, utricaria or allergic type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such.
Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG surgery).

WARNINGS AND SPECIAL PRECAUTIONS FOR USE:

WARNING
RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms. in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of puberty not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Patients with risk factors of heart disease, hypertension, hyperlipidaemia.diabetes mellitus,smoking patients and patients with peripheral arterial disease should only be treated with celecoxib after careful consideration.
Cardiovascular Effects
Cardiovascular Thrombotic Events: Celecoxib may cause an increased risk of serious cardiovascular (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, duration of use and baseline cardiovascular risk factors. Patients with known medical history of cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular 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 cardiovascular symptoms. Patients should be informed about the signs and symptoms of serious cardiovascular toxicity and the steps to take if they occur.
Celecoxib is not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, anti-platelet therapies (e.g., acetylsalicylic acid) 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 cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. 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.
*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 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. These serious adverse events can occur at any time with or without warning symptoms, in patients treated with NSAIDs. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly. patients with cardiovascular 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. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking,use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events have been in elderly or debilitated patients. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during celecoxib therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.
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 administeredCelecoxib.
Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib.
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. Celecoxibshould be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class 13), and initiated at half the recommended dose.
Rare cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), Over 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.
General
By reducing inflammation, celecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections.
The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.
CYP 2D6 inhibition
Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated drugs that are metabolised by CYP2D6.

INTERACTIONS WITH OTHER MEDICAMENTS:
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 otherCYP2C9 substrates should be administered celecoxibwith caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended close.
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. Conical 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:
Lithium: In healthy subjects, lithium plasma levels increased approximately 17% in subjects receiving lithium together withcelecoxib. 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. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin in the prophylactic treatment of cardiovascular disease.
Anti-hypertensives including Angiotensin-converting enzyme inhibitors **(ACE1s), Anglotensln 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.
Cyclosporine: Because of their effect on renal prostaglandins. NSAIDs may increase the risk of nephrotoxicity with cyclosporine.
Fluconazole and ketoconazole: Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib of 60% and in AUC of 130%. Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevantinhibition in the metabolism of celecoxib.
Dextromethorphan and metoprolol: Concomitant administration ofcelecoxib 200 mg twice day resuited in a 2.6-fold and a 1.5-fold increases in plasma concentrations of dextromethorphan andmetoprolol (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.
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 clinicaly relevant effects on the pharmacokinetics of a prototype combination oral contraceptive(1 mg norethindrone/ 0.035 mgethinyl estradio1).
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:
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.
Pregnancy:
There are no studies in pregnant women. Studies in animals have shown reproductive toxicity. The relevance of these data for humans is unknown. Celecoxib, as with other drugs inhibiting prostaglandin Synthesis, map cause uterine inertia and premature closure of the ductusarteriosus 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.
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.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.
UNDESIRABLE EFFECTS:
Adverse reactions are listed by system organ class in Table 1, reflecting data from already reported lit erature.
Table 1. Adverse Drug Reactions (ADRs)#reported in existing literature.

System Organ Class Frequency	Adverse Drug Reactions
Infections and infestations Common Uncommon	 Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection Pharyngitis, rhinitis
Blood and lymphatic system disorders Uncommon Rare	 Anaemia Thrombocytopenia
Immune system disorders Uncommon	 Hyper-sensitivity
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	 Palpitations, Cardiac failure congestive, arrhythmia, tachycardia
Vascular disorders Common Rare	 Hypertension(including aggravated hypertension) Flushing
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 (including alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders Common Uncommon Rare Very Rare	 Pruritus (includes pruritus generalised), rash Urticaria, ecchymosis Angioedema, alopecia Dermatitis bullous
General disorders and administrative site conditions Common Uncommon	 Oedema peripheral edema Face oedema, influenza-like illness
Injury, poisoning and procedural complications Uncommon	 Injury

These adverse reactions are reported in already existing data of Innovator of Celecoxib Capsules.
OVERDOSE AND TREATMENT:
Clinical experience of overdose is not reported in existing data. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects for nine days without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment. Dialysis is unlikely to be an efficient method of drug removal due to high protein binding.
DOSAGE FORM AND PACKAGING AVAILABLE:
Dosage Form : Capsule
Packing : 3 x 10 & 10 x 10 Alu-Alu Blister pack.
SHELF LIFE
36 months
STORAGE: Store below 30°C.
Keep the medicine out of reach of children.
Manufactured in India by:
GRACURE PHARMACEUTICALS LTD.
E-1105, Industrial Area, Phase III, Bhiwadi, Alwar (Rajasthan).
HEALOL PHARMACEUTICALS SDN. BHD
74-3, Jalan Wangsa Delima 6,
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