

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

Celebib 100 / 200 (Celecoxib Capsules 100 mg / 200 mg)

COMPOSITION

Celebib 100 :

Each capsule contains:
Celecoxib Ph. Eur100 mg

Celebib 200 :

Each capsule contains:
Celecoxib Ph. Eur200 mg

PRODUCT DESCRIPTION

Celebib 100 : Size '4' Capsule, containing white to off-white powder, having white opaque cap, white opaque body with 'C5' imprinted on a blue band on the cap and '100 mg' imprinted on a blue band on the body.

Celebib 200 : Size '2' Capsule, containing white to off-white powder, having white opaque cap, white opaque body with 'C6' imprinted on a yellow band on the cap and '200 mg' imprinted on a yellow band on the body.

PHARMACOLOGICAL CLASSIFICATION

Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs,

ATC Code : M01AH01

PHARMACOLOGICAL ACTION:

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 is about 97 % at therapeutic plasma concentrations and the medicinal product is not preferentially bound to erythrocytes.

Biotransformation

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 i.e., 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.

Elimination

Celecoxib is mainly eliminated by metabolism. Less than 1 % of the dose is excreted unchanged in urine. The inter-subject variability in the exposure of celecoxib is about 10-fold. Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment.

PHARMACODYNAMICS:

Mechanism of action

Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

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 ductus arteriosus, 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 humans 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. sulfamethoxazole and other sulfonamide antibiotics).

A dose-dependent effect on TxB2 formation has been observed after high doses of celecoxib.

INDICATIONS AND USAGE

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 (100 mg and 200 mg only)

DOSAGE AND ADMINISTRATION

Posology and method of 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): The recommended 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 Dysmenorrhoea: 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 Special Warnings and Special Precautions for Use - 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 (see Special Warnings and Special Precautions for Use – Renal Effects).

Children: Celecoxib is not indicated for use in children.

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 dose to half the lowest recommended dose.

CONTRAINDICATIONS

Celecoxib is contraindicated:

- Hypersensitivity to the active substance or to any of the excipients.
- Known hypersensitivity to sulphonamides.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Contraindication for patients who have increased risk of cardiovascular disease (ischaemic heart disease and stroke).
- In pregnancy and in women of childbearing potential unless using an effective method of contraception. Celecoxib has been shown to cause malformations in the two animal species studied. The potential for human risk in pregnancy is unknown, but cannot be excluded.
- Breast-feeding.
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10).
- Patients with estimated creatinine clearance <30 ml/min.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

ADVERSE REACTION

Following side effects are seen :

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection			
Blood and lymphatic system disorders			Anaemia	Leukopenia, Thrombocytopenia	Pancytopenia ⁴
Immune System disorders		Hyper-sensitivity			Anaphylactic shock ⁴ , anaphylactic reaction ⁴
Metabolism and nutrition disorders			Hyperkalaemia		
Psychiatric disorders		Insomnia	Anxiety, depression, fatigue	Confusional state, hallucinations ⁴	
Nervous System disorders		Dizziness, hypertonia, headache ⁴	Cerebral infarction ¹ , paraesthesia, somnolence	Ataxia, dysgeusia	Haemorrhage Intracranial (including fatal intracranial haemorrhage) ⁴ , meningitis aseptic ⁴ , epilepsy (including aggravated epilepsy) ¹ , ageusia ⁴ , anosmia ⁴
Eye disorders			Vision blurred, conjunctivitis ⁴	Eye haemorrhage ⁴	Retinal artery occlusion ⁴ , retinal vein occlusion ⁴
Ear and labyrinth disorders			Tinnitus, hypoacusis ¹		
Cardiac disorders		Myocardial infarction ¹	Cardiac failure, palpitations, tachycardia	Arrhythmia ⁴	
Vascular disorders	Hyper-tension ¹ (including aggravated hyper-tension)			Pulmonary embolism ¹ , flushing ⁴	Vasculitis ⁴
Respiratory, thoracic, and mediastinal disorders	Rhinitis, dyspnoea ¹	cough,	Bronchospasm ⁴	Pneumonitis ⁴	
Gastrointestinal disorders	Nausea ⁴ , abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting ¹ , dysphagia ⁴		Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of large intestinal inflammation), eructation	Gastro-intestinal haemorrhage ⁴ , duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, and large intestinal perforation; oesophagitis, melena; pancreatitis, colitis ⁴	
Hepatobiliary disorders			Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT)	Hepatitis ⁴	Hepatic failure ⁴ (sometimes fatal or requiring liver transplant), hepatitis fulminant ⁴ (some with fatal outcome), hepatic necrosis ⁴ , cholestasis ⁴ , hepatitis cholestatic ⁴ , jaundice ⁴
Skin and Subcutaneous Tissue disorders	Rash, pruritus (includes Pruritus generalised)		Urticaria, ecchymosis ⁴	Angioedema ⁴ , alopecia, photosensitivity	Dermatitis exfoliative ⁴ , Erythema multiforme ⁴ , Stevens-Johnson syndrome ⁴ , toxic epidermal necrolysis ⁴ , drug reaction with eosinophilia and systemic symptoms (DRESS) ⁴ , acute generalised exanthematous pustulosis (AGEP) ⁴ , dermatitis bullosa ⁴
Musculoskeletal and connective tissue disorders		Arthralgia ⁴	Muscle spasms (leg cramps)		Myositis ⁴
Renal and urinary disorders			Blood Creatinine increased, blood urea increased	Renal failure acute ⁴ , hyponatraemia ⁴	Interstitial nephritis ⁴ , nephritic syndrome ⁴ , glomerulonephritis ⁴ , minimal lesion ⁴
Reproductive system and breast disorders				Menstrual disorder ⁴	
General disorders and administrative site conditions		Influenza-like illness, Oedema peripheral/retention	Face oedema, chest pain ⁴		
Injury, poisoning and procedural complications		Injury (accidental injury)			

DRUG INTERACTIONS

Pharmacodynamic interactions

Anticoagulants

Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed. Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin, some of them fatal.

Anti-hypertensives

NSAIDs may reduce the effect of anti-hypertensive medicinal products including ACE inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics, or elderly patients) when ACE inhibitors, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including celecoxib. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Ciclosporin and Tacrolimus

Coadministration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when celecoxib and any of these drugs are combined.

Acetylsalicylic acid

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.

Pharmacokinetic interactions

Effects of celecoxib on other drugs

CYP2D6 Inhibition

Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of drugs that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of drugs which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic drugs, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated. Concomitant administration of celecoxib 200 mg twice daily resulted in 2.6-fold and 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib CYP2D6 inhibition of the CYP2D6 substrate metabolism.

CYP2C19 Inhibition

In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this *in vitro* finding is unknown. Examples of drugs which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate

In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.

Lithium

In healthy subjects, co-administration of celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in C_{max} of 16% and in AUC of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Oral contraceptives

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone /35 micrograms ethinylestradiol). Glibenclamide/tolbutamide Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.

Effects of other drugs on celecoxib

CYP2C9 Poor Metabolisers

In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers.

CYP2C9 Inhibitors and Inducers

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 C_{max} of 60% and in AUC of 130%. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole and Antacids

Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

Paediatric population

Interaction studies have only been performed in adults.

WARNINGS & PRECAUTIONS

Gastrointestinal (GI) effects

Upper and lower gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. 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.

Concomitant NSAID use

The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

Cardiovascular effects

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis. When prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease, Patients should only be treated with celecoxib after careful consideration.

Fluid retention and oedema

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

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. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

Hepatic and renal effects

Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

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, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.

Some 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. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment. If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of celecoxib therapy should be considered.

CYP2D6 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.

CYP2C9 poor metabolisers

Patients known to be CYP2C9 poor metabolisers should be treated with caution.

Skin and systemic hypersensitivity 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 reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome), have been reported in patients receiving celecoxib. Patients with a history of sulphonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General

Celecoxib may mask fever and other signs of inflammation.

Use with oral anticoagulants

In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported. Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with celecoxib is initiated or celecoxib dose is changed. Concomitant use of anticoagulants with NSAIDs may increase the risk of bleeding. Caution should be exercised when combining celecoxib with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

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 patients 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.

PREGNANCY

Pregnancy

Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations. 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. The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester.

During the second or third trimester of pregnancy, NSAIDs including celecoxib 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.

Celecoxib is contraindicated in pregnancy and in women who can become pregnant. If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Breast-feeding

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. Women who take Celecoxib should not breastfeed.

DRIVING AND USING MACHINES :

Patients who experience dizziness, vertigo or somnolence while taking Celebix should refrain from driving or operating machinery.

OVERDOSAGE

There is no clinical experience of overdose. 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.

STORAGE

Store below 30°C in a dry place. Protect from light.

PRESENTATION

- 1) Alu-PVC/PVdC Blister of 10's and such 3 blisters packed in a carton along with pack insert.
- 2) Alu-PVC/PVdC Blister of 10's and such 10 blisters packed in a carton along with pack insert.



MANUFACTURED BY

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Date of Revision : 11 April 2023.