

Proposed Professional Information for CELECOXIB BIOTECH

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CELECOXIB 100 mg BIOTECH, hard capsules

CELECOXIB 200 mg BIOTECH, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELECOXIB 100 BIOTECH capsule contains 100 mg celecoxib.

Each CELECOXIB 200 BIOTECH capsule contains 200 mg celecoxib.

Excipients with known effect:

Contains sugar.

CELECOXIB 100 BIOTECH: Each capsule contains 25 mg lactose monohydrate.

CELECOXIB 200 BIOTECH: Each capsule contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

1.3.1.1

CELECOXIB 100 BIOTECH: Hard gelatin capsules, size “3”, imprinted with “135” on the opaque white body in blue ink and “A” on the opaque white cap in blue ink, filled with white to off-white coloured granular powder.

CELECOXIB 200 BIOTECH: Hard gelatin capsules, size “1”, imprinted with “136” on the opaque white body in golden yellow ink and “A” on the opaque white cap in golden yellow ink, filled with white to off-white coloured granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Symptomatic treatment of inflammation and pain in osteoarthritis and rheumatoid arthritis.
- Treatment of pain after dental surgery.
- Treatment of mild to moderate post-operative pain.
- Treatment of mild to moderate musculoskeletal pain.
- Treatment of mild to moderate primary dysmenorrhoea.
- Relief of symptoms of ankylosing spondylitis.

4.2 Posology and method of administration

Posology

As the cardiovascular risks of CELECOXIB BIOTECH may increase with dose and duration of exposure, the lowest effective daily dose should be used, for the shortest possible duration of treatment.

Osteoarthritis

The recommended daily dose is 200 mg, taken as a single dose or as two divided doses. Doses up to 400 mg per day have been studied.

Rheumatoid arthritis

The recommended daily dose is 100 mg or 200 mg twice per day.

Pain post-dental surgery

The recommended dose is 100 mg to 200 mg, up to a maximum daily dose of 400 mg. Dosing intervals should not be less than 4 hours.

Mild to moderate post-operative pain

The recommended dose is 200 mg once daily. Some patients may benefit from an additional 200 mg dose.

Mild to moderate musculoskeletal pain

The recommended dose is 200 mg twice daily.

Mild to moderate primary dysmenorrhoea

The recommended dose is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily.

Ankylosing spondylitis

The recommended daily dose is 200 mg, taken as a single dose or as 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

Special populations

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. Introduce CELECOXIB BIOTECH at the lowest recommended dose in patients with moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment (see

sections 4.3 and 5.2).

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 sections 4.3 and 5.2).

Elderly

No dosage adjustment is necessary. However for elderly patients with a body mass of 50 kg or less it is advisable to initiate therapy at the lowest recommended dose.

Children

As no data are available, CELECOXIB BIOTECH is not recommended in persons under 18 years old.

Method of administration

Oral use. CELECOXIB BIOTECH should be taken whole with a glass of water, with or without food.

4.3 Contraindications

- Hypersensitivity to celecoxib, or any other excipient of CELECOXIB BIOTECH (see section 6.1).
- Known hypersensitivity to sulphonamide.
- Severe hepatic impairment (serum albumin < 25 g/L or Child-Pugh score > 10).
- Severe renal impairment with estimated creatinine clearance < 30 mL/min.

- Asthma, urticaria or allergic-type reactions precipitated by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase 2 (COX-2) specific inhibitors.
- Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Perioperative analgesia against the background of coronary artery bypass surgery (CABG).
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Inflammatory bowel disease.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception (see section 4.6). The potential for human risk in pregnancy is unknown but cannot be excluded.
- Breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

CELECOXIB BIOTECH may predispose to cardiovascular incidents, cerebrovascular incidents, gastrointestinal events or cutaneous reactions that may be fatal.

Safety and efficacy of CELECOXIB BIOTECH have not been established for treatment exceeding 12 weeks in osteoarthritis and 24 weeks in rheumatoid arthritis.

Cardiovascular effects

Increased number of serious cardiovascular (CV) events, mainly myocardial infarction, has been reported in patients with sporadic adenomatous polyps treated with celecoxib (as in CELECOXIB BIOTECH) at doses of 200 mg twice daily and 400 mg twice daily, compared to placebo (see section 5.1).

As the cardiovascular risks of CELECOXIB BIOTECH may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1).

Caution is advised when CELECOXIB BIOTECH is prescribed to patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

CELECOXIB BIOTECH is not a substitute for aspirin for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Anaphylactoid reactions

As with NSAIDs in general, anaphylactoid reactions occurred in patients exposed to CELECOXIB BIOTECH (see sections 4.3).

Gastrointestinal (GI) effects

Upper and lower gastrointestinal complications (perforations, ulcers or bleedings (PUBs)), some resulting in fatalities, have occurred in patients treated with celecoxib (as in CELECOXIB

BIOTECH). 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 antiplatelet medicine (such as aspirin) or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of or active gastrointestinal disease, such as ulceration and GI bleeding.

When CELECOXIB BIOTECH is taken concomitantly with aspirin (even at low doses), there is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications).

A significant difference in GI safety between selective COX-2 inhibitors plus aspirin vs NSAIDs plus aspirin has not been demonstrated in long-term clinical trials.

Concomitant NSAID use

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

Fluid retention and oedema

Fluid retention and oedema have been observed in patients taking celecoxib (as in CELECOXIB BIOTECH). Therefore, CELECOXIB BIOTECH 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.

Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Hypertension

NSAIDs, including celecoxib (as in CELECOXIB BIOTECH) 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 BIOTECH 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 BIOTECH, may cause renal toxicity. Celecoxib has 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, angiotensin converting enzyme (ACE)-inhibitors, angiotensin II receptor antagonists, and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with CELECOXIB BIOTECH.

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 (contained in CELECOXIB BIOTECH). Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib (contained in CELECOXIB BIOTECH) treatment (see section 4.8).

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of CELECOXIB BIOTECH therapy should be considered.

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

CYP2D6 inhibition

Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction of CELECOXIB BIOTECH may be necessary for individually dose-titrated medicines that are metabolised by CYP2D6 (see section 4.5).

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, (as in CELECOXIB BIOTECH) see section 4.8.

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. 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 (as in CELECOXIB BIOTECH), see section 4.8. Patients with a history of sulphonamide allergy or any medicine allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). CELECOXIB BIOTECH should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as CELECOXIB BIOTECH. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue CELECOXIB BIOTECH and evaluate the patient immediately.

General

CELECOXIB BIOTECH 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 (see sections 4.8 and 4.5).

Because increases in prothrombin time (INR) have been reported, anticoagulant activity should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with CELECOXIB BIOTECH is initiated, or its dose is changed (see section 4.5).

Concomitant use of anticoagulants with NSAIDs may increase the risk of bleeding. Caution should be exercised when combining CELECOXIB BIOTECH with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipients

CELECOXIB BIOTECH contains lactose monohydrate (see sections 2 and 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose/galactose malabsorption should not take CELECOXIB BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Anticoagulants

In patients on concurrent therapy with warfarin, increases in prothrombin time (INR) have been reported (see section 4.4).

Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of CELECOXIB BIOTECH 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 BIOTECH is initiated or the dose is changed (see section 4.4). Bleeding events in association with increases in prothrombin time (INR) have been reported, predominantly in the elderly, in patients receiving celecoxib (as in CELECOXIB BIOTECH) concurrently with warfarin, some of them fatal.

Antihypertensives

NSAIDs, including CELECOXIB BIOTECH, may reduce the effect of antihypertensive medicines (including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers). This interaction should be given consideration in patients taking CELECOXIB BIOTECH concomitantly with antihypertensive medicines. 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 or angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including CELECOXIB BIOTECH (see section 4.4). 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.

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ciclosporin and tacrolimus

Co-administration of NSAIDs (including CELECOXIB BIOTECH) and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when CELECOXIB BIOTECH and any of these medicines are combined.

Aspirin

CELECOXIB BIOTECH can be used with low-dose aspirin. However, concomitant administration of aspirin with CELECOXIB BIOTECH may result in an increased risk of gastrointestinal ulceration or other gastrointestinal complications, compared to use of CELECOXIB BIOTECH alone. Because of its lack of platelet effects, CELECOXIB BIOTECH is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thromboembolic events associated with CELECOXIB BIOTECH.

An increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of CELECOXIB BIOTECH alone was shown for concomitant administration of low-dose aspirin.

Pharmacokinetic interactions

Effects of CELECOXIB BIOTECH on other medicines

CYP2D6 inhibition

Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicines that are substrates of this enzyme may be increased when CELECOXIB BIOTECH is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and selective serotonin reuptake inhibitors (SSRIs)), neuroleptics, antidysrhythmic medicines, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with CELECOXIB BIOTECH is initiated or increased if treatment with CELECOXIB BIOTECH 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 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 medicines 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 medicines.

Lithium

In healthy persons, 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 area under the curve (AUC) of 18 % of lithium. Therefore, patients on lithium treatment should be closely monitored when CELECOXIB BIOTECH is introduced or withdrawn.

Oral contraceptives

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptive (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.

Phenytoin

In specific studies in healthy volunteers with other medicines metabolised by CYP2C9, celecoxib was found to produce no clinically significant pharmacokinetic interaction with phenytoin.

Effects of other medicines on CELECOXIB BIOTECH

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 (see section 4.4).

CYP2C9 inhibitors and inducers

Since celecoxib is predominantly metabolised by CYP2C9, CELECOXIB BIOTECH 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 populations

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

1.3.1.1

CELECOXIB BIOTECH is contraindicated in pregnancy (see section 4.3).

Regular use of NSAIDs during pregnancy may result in:

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Second and Third trimester

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligohydroamniosis. At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

Breastfeeding

Limited data indicate that CELECOXIB BIOTECH is excreted in breastmilk and therefore should not be used during lactation.

Fertility

Based on the mechanism of action, the use of NSAIDs, including CELECOXIB BIOTECH, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence (see section 4.8) while taking CELECOXIB BIOTECH should refrain from driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Infections and infestations	
<i>Frequent:</i>	sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection, bronchitis
<i>Less frequent:</i>	helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection
Blood and lymphatic system disorders	
<i>Less frequent:</i>	anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis, ecchymosis
Immune system disorders	
<i>Frequent:</i>	hypersensitivity, allergy aggravated
<i>Less frequent:</i>	anaphylactic shock, anaphylactic reaction, angioedema
<i>Frequency unknown:</i>	anaphylaxis

Metabolism and nutrition disorders

Frequent: increased weight

Less frequent: hyperkalaemia, increased blood sodium

Psychiatric disorders

Frequent: insomnia

Less frequent: anxiety, depression, fatigue, confusional state, hallucinations

Nervous system disorders

Frequent: dizziness, hypertonia, headache

Frequency unknown: cerebral infarction (stroke), paraesthesia, somnolence, ataxia, dysguesia, intracranial haemorrhage (including fatal intracranial haemorrhage), aseptic meningitis, epilepsy (including aggravated epilepsy), ageusia, anosmia

Eye disorders

Less frequent: blurred vision, conjunctivitis, eye haemorrhage, retinal artery occlusion, retinal vein occlusion, vitreous floaters, conjunctival haemorrhage

Ear and labyrinth disorders

Less frequent: tinnitus, hypoacusis, dysphonia

Cardiac disorders

Frequent: myocardial infarction, angina pectoris

Less frequent: cardiac failure, palpitations, tachycardia, dysrhythmia

Frequency unknown: cardiovascular thrombotic incidents

Vascular disorders

Frequent: hypertension (including aggravated hypertension)

Less frequent: pulmonary embolism, flushing, vasculitis, deep vein thrombosis

Respiratory, thoracic and mediastinal disorders

Frequent: rhinitis, cough, dyspnoea

Less frequent: bronchospasm, pneumonitis

Gastrointestinal disorders

Frequent: nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia, irritable bowel syndrome, tooth disorder

Less frequent: constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation, gastrointestinal haemorrhage, duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, pancreatitis, colitis, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration

Hepatobiliary disorders

Less frequent: abnormal hepatic function, increased hepatic enzymes (including increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), hepatitis, hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), hepatic necrosis, cholestasis, cholestatic jaundice

Skin and subcutaneous tissue disorders

Frequent: rash, pruritis (includes pruritis generalised)

Less frequent: urticaria, ecchymosis, alopecia, photosensitivity, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), bullous dermatitis, lipoma, allergic dermatitis, ganglion

Musculoskeletal and connective tissue disorders

Frequent: arthralgia

Less frequent: muscle spasms (leg cramps), myositis, lower limb fracture

Renal and urinary disorders

Less frequent: increased blood creatinine, increased blood urea, acute renal failure, hyponatraemia, tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion, nephrolithiasis, nocturia

Reproductive system and breast disorders

Less frequent: menstrual disorder

Frequency unknown: female infertility (female fertility decreased), vaginal haemorrhage, breast tenderness

General disorders and administration site conditions

Frequent: influenza-like illness, peripheral oedema/fluid retention

Less frequent: face oedema, chest pain

Injury, poisoning and procedural complications

Frequent: accidental injury

Description of selected adverse reactions

In final data (adjudicated) from the APC and PreSAP trials in patients treated with celecoxib 400 mg daily for up to 3 years (pooled data from both trials), the excess rate over placebo for myocardial infarction was 7,6 events per 1 000 patients (less frequent) and there was no excess rate for stroke (types not differentiated) over placebo.

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the “**6.04 Adverse Drug Reaction Reporting Form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>.

4.9 Overdose

There is no clinical experience of overdose. Single doses up to 1 200 mg and multiple doses up to 1 200 mg twice daily have been administered to healthy persons without clinically significant adverse effects. In the event of a suspected overdose, appropriate supportive medical care should be provided. Dialysis is not likely to be an efficient method of medicine removal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs

ATC code: M01AH01.

Celecoxib is a specific cyclooxygenase 2 (COX-2) inhibitor (SCI). Cyclooxygenase-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, particularly prostaglandin E₂, causing inflammation, oedema and pain.

Celecoxib acts as an anti-inflammatory, analgesic and anti-pyretic medicine by blocking the production of inflammatory prostanoids via COX-2 inhibition.

Celecoxib has a very low affinity for the constitutively expressed cyclooxygenase -1 enzyme (COX-1).

5.2 Pharmacokinetic properties

Absorption

When given under fasting conditions celecoxib reaches peak plasma concentrations after approximately 2 – 3 hours.

Celecoxib exhibits linear and dose proportional pharmacokinetics over the therapeutic dose range.

Plasma protein binding is concentration independent and is about 97 % at therapeutic plasma concentrations and the medicine is not preferentially bound to erythrocytes in the blood.

Taking a dose with food (a high fat meal) delays absorption, resulting in a T_{max} of about 4 hours, and increases bioavailability by about 20 %.

Biotransformation

Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation. It was demonstrated that celecoxib is predominantly metabolised by cytochrome P450 CYP2C9. Pharmacological activity resides in the parent medicine. The main metabolites found in the circulation have no detectable COX-1 or COX-2 inhibitory activity.

Elimination

Celecoxib is mainly eliminated by hepatic metabolism with less than 1 % of the dose excreted unchanged in urine. After multiple dosing, the elimination half-life is 8 – 12 hours and the rate of clearance about 500 mL/min. With multiple dosing steady state plasma concentrations are reached before day 5.

Variability among patients 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 after a single 200 mg dose, indicating wide distribution of celecoxib into the tissues. Pre-clinical studies indicate that celecoxib crosses the blood/brain barrier.

Special populations

Hepatic impairment

Plasma concentrations of celecoxib in patients with mild hepatic impairment are not significantly different from those of age and sex matched controls. In patients with moderate hepatic impairment celecoxib plasma concentrations are about twice those of matched controls. Patients with severe hepatic impairment have not been studied but can be expected to show accumulation of parent substance, as the main route of metabolism is via the liver.

Renal impairment

In elderly volunteers with age-related reductions in glomerular filtration rate (GFR) (mean GFR > 65 mL/min per 1,73 m²) and in patients with chronic stable renal insufficiency (GFR 35 – 60 mL/min per 1,73 m²), celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance.

Renal effects

The relative roles of COX-1 and COX-2 in renal physiology are not clear. CELECOXIB BIOTECH reduces the urinary excretion of PGE₂ and 6-keto-PGF_{1α} (a prostacyclin metabolite) but leaves serum thromboxane B₂ (TXB₂) and urinary excretion of 11-dehydro-TXB₂, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown that CELECOXIB BIOTECH produces no decrease in GFR in the elderly or those with chronic renal insufficiency. These studies have also shown transient reductions in fractional excretion of sodium.

Elderly patients 65 years and older

In the population > 65 years there is a two-fold increase in mean C_{max} and AUC for celecoxib. This is a predominantly weight-related rather than age-related change. Celecoxib levels are higher in lower weight individuals and therefore higher in the elderly population who are generally of lower mean weight than the younger population. Elderly females therefore tend to have slightly higher celecoxib plasma concentrations than elderly males.

Children

Celecoxib has not been studied in patients under 18 years old.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate (E572)

Povidone (E1201)

Sodium lauryl sulfate

Capsule shell:

Gelatin

Titanium dioxide (E171)

Printing ink:

CELECOXIB 100 BIOTECH:

FD&C blue No. 1 Aluminium lake (E132)

Propylene glycol (E1520)

Shellac

CELECOXIB 200 BIOTECH:

Biotech Laboratories (Pty) Ltd
500438/9
Date of submission: 15 September 2021

CELECOXIB 100 BIOTECH (100 mg capsules, hard)
CELECOXIB 200 BIOTECH (200 mg capsules, hard)

Propylene glycol (E1520)

Shellac

Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Transparent PVC/PE/PVDC and silver aluminium foil blister strips placed in an outer carton.

Silver aluminium/aluminium blister strips placed in an outer carton.

Pack sizes:

CELECOXIB 100 BIOTECH: 60 capsules

CELECOXIB 200 BIOTECH: 10, 15 or 30 capsules.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central park

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBERS

CELECOXIB 100 BIOTECH: Will be allocated by SAHPRA upon registration.

CELECOXIB 200 BIOTECH: Will be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Will be allocated by SAHPRA upon registration.

10. DATE OF REVISION OF THE TEXT

15 September 2021