PROPOSED PROFESSIONAL INFORMATION FOR CELEXII

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CELEXII 100 hard gelatine capsules

CELEXII 200 hard gelatine capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELEXII 100 capsule contains 100 mg celecoxib.

Each CELEXII 200 capsule contains 200 mg celecoxib.

Excipient with known effect:

CELEXII 100 contains sugar (lactose monohydrate, 20,83 mg)

CELEXII 200 contains sugar (lactose monohydrate, 41,65 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules

CELEXII 100: An opaque blue, size 3, hard gelatine capsule, 1308 imprinted with black ink on the cap and 100 imprinted with black ink on the body, containing a white to off-white granular powder.

CELEXII 200: An opaque yellow, size 1, hard gelatine capsule, 1309 imprinted with black ink on the cap and 200 imprinted with black ink on the body, containing a white to off-white 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 CELEXII 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, administered as a single dose or as 100 mg twice daily.

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 CELEXII 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, CELEXII is not recommended in persons under 18 years old.

Method of administration:

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

4.3 Contraindications

- Hypersensitivity to celecoxib, or any other excipient of CELEXII (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 non-steroidal 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.
- Peri-operative 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

CELEXII may predispose to cardiovascular incidents, cerebrovascular incidents,

gastrointestinal events or cutaneous reactions that may be fatal.

Safety and efficacy of CELEXII 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 CELEXII) at doses of 200 mg twice daily and 400 mg twice daily, compared to placebo (see section 5.1).

As the cardiovascular risks of CELEXII 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 CELEXII is prescribed to patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

CELEXII 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 have occurred in patients exposed to CELEXII (see section 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 CELEXII). 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 medicines (such as aspirin) or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.
When CELEXII 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 CELEXII 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 CELEXII). Therefore, CELEXII 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 CELEXII) 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 CELEXII 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 CELEXII, 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 CELEXII.

Severe hypokalaemia and renal tubular acidosis (RTA) have been reported with the prolonged use of other NSAIDs (such as ibuprofen) at higher than recommended doses. Caution is advised with the use of CELEXII.

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 CELEXII). 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 CELEXII) 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 CELEXII 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 CELEXII therapy.

CYP2D6 inhibition

Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction of CELEXII 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 in association with the use of celecoxib (as in CELEXII), 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 reaction with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome), have been reported in patients receiving celecoxib (as in CELEXII), 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).

CELEXII should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as CELEXII. 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 CELEXII and evaluate the patient immediately.

General

CELEXII may mask fever and other signs of inflammation.

Use with oral anticoagulants

In patients on concurrent therapy with warfarin, serious bleeding events, of which some were 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 CELEXII 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 CELEXII with warfarin or other oral anticoagulants, including novel anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban).

Excipient warnings:

CELEXII 100 mg and 200 mg 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 CELEXII.

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 CELEXII 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 CELEXII is initiated or its 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 CELEXII) concurrently with warfarin, some of them fatal.

Anti-hypertensives

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

Aspirin

CELEXII can be used with low-dose aspirin. However, concomitant administration of aspirin with CELEXII may result in an increased rate of GI ulceration or other complications, compared to use of CELEXII alone. Because of its lack of platelet effects, CELEXII 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 thrombotic events associated with CELEXII.

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

Pharmacokinetic interactions

Effects of CELEXII 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 CELEXII is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, antidysrhythmic medicines, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with CELEXII is initiated or increased if treatment with CELEXII 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 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 CELEXII 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.

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 CELEXII

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, CELEXII 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:

CELEXII is contraindicated in pregnancy (see section 4.3).

Regular use of non-steroidal inflammatory drugs 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 oligo-hydroamniosis.

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 CELEXII is excreted in breast milk and must therefore not be used during lactation.

Fertility

Based on the mechanism of action, the use of NSAIDs, including CELEXII, 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 CELEXII should refrain from driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions:

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection, bronchitis
	Less frequent	Helicobacter infection, herpes zoster, erysipelas,

		bronchopneumonia, labyrinthitis, gingival infection
Blood and the lymphatic system disorders	Less frequent	Anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis, ecchymosis
Immune system disorders	Frequent Less frequent Frequency unknown	Hypersensitivity, allergy aggravated Anaphylactic shock, anaphylactic reaction, angioedema Anaphylaxis
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Increased weight Hyperkalaemia, increased blood sodium Hypokalaemia
Psychiatric disorders	Frequent Less frequent	Insomnia Anxiety, depression, fatigue, confusional state, hallucinations
Nervous system disorders	Frequent Frequency unknown	Dizziness, hypertonia, headache Cerebral infarction (stroke), paraesthesia, somnolence, ataxia, dysgeusia, 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 Less frequent Frequency unknown	Myocardial infarction, angina pectoris Cardiac failure, palpitations, tachycardia, dysrhythmia Cardiovascular thrombotic incidents
Vascular disorders	Frequent Less frequent	Hypertension (including aggravated hypertension) Pulmonary embolism, flushing, vasculitis, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Rhinitis, cough, dyspnoea Bronchospasm, pneumonitis
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia, irritable bowel

	Less frequent	syndrome, tooth disorder 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
Hepato-biliary disorders	Less frequent	Abnormal hepatic function, increased hepatic enzymes (including increased AST and 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 Less frequent	Rash, pruritus (includes generalised pruritus) 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 Less frequent	Arthralgia Muscle spasms (leg cramps), myositis, lower limb fracture
Renal and urinary disorders	Less frequent Frequency unknown	Increased blood creatinine, increased blood urea, acute renal failure, hyponatraemia, tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion, nephrolithiasis, nocturia Renal tubular acidosis
Reproductive system and	Less frequent Frequency unknown	Menstrual disorder Female infertility (female

breast disorders		fertility decreased), vaginal haemorrhage, breast tenderness
General disorders and administration site conditions	Frequent Less frequent	Influenza-like illness, peripheral oedema/fluid retention 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 of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions 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 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 medicine removal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Category A, class 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 is absorbed reaching 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 mostly 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. Preclinical 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 1,73 m^2) and in patients with chronic stable renal insufficiency (GFR 35 – 60 mL/min/1,73 m^2) 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. CELEXII reduces the urinary excretion of PGE2 and 6-ketoPGF1α (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 that CELEXII 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 2-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 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

Granular powder:

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Povidone K-30

Sodium lauryl sulphate

CELEXII 100 Capsule:

Carmoisine

Gelatine

Patent blue V

Sodium lauryl sulphate

Titanium dioxide

CELEXII 200 Capsule:

Gelatine

Iron oxide yellow

Sodium lauryl sulphate

Titanium dioxide

Printing ink:

Black iron oxide

Potassium hydroxide

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

White, opaque PVC/PVdC-Alu blister strips.

Each blister strip contains 10 capsules.

Pack sizes: 30s and 60s.

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

Activo Health (Pty) Ltd.

Block B, Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBERS

CELEXII 100: 50/3.1/9029

CELEXII 200: 50/3.1/9030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 12 October 2021

10. DATE OF REVISION OF THE TEXT

TBC