Approved Professional Information for Medicines for Human Use:

XIBECIL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

XIBECIL 100 mg capsules

XIBECIL 200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XIBECIL 100 mg: Each hard gelatin capsule contains 100 mg celecoxib.

XIBECIL 200 mg: Each hard gelatin capsule contains 200 mg celecoxib.

Contains sugar (lactose monohydrate).

Each 100 mg hard gelatin capsule contains 27,07 mg of lactose monohydrate.

Each 200 mg hard gelatin capsule contains 54,14 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

XIBECIL 200 mg

Hard Gelatin Capsule Size “2” opaque white with blue band reverse printed “100” in white on body and “CEL” in white on cap filled with white to off-white colored granular powder.

XIBECIL 200 mg

Hard Gelatin Capsules Size “2” opaque white with yellow band reverse printed “200” in white on body and “CEL” in white on cap filled with white to off-white colored granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Symptomatic treatment of inflammation and pain in osteoarthritis and rheumatoid arthritis.
- Treatment of pain post 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 signs and symptoms of ankylosing spondylitis.

4.2 Posology and method of administration

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

Posology

Osteoarthritis

The recommended daily dose is 200 mg, administered 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 dysmenorrhea

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 per day.

Some patients may benefit from a total daily dose of 400 mg.

Special populations

Elderly population

No dosage adjustment is 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.

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 section 4.3).

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. Introduce XIBECIL at the lowest recommended dose in patients with moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment (see section 4.3).

Paediatric population

XIBECIL is not indicated for use in children under 18 years old.

Method of administration

XIBECIL is for oral administration and may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to celecoxib or to any of the excipients listed in section 6.1.

- Known sulphonamide hypersensitivity.
- Severe impairment of hepatic function.
- Severe impairment of renal function.
- Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Peri-operative analgesia in the setting of coronary artery bypass surgery (CABG).
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic type reactions after taking acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception (see section 4.6).
- Celecoxib has been shown to cause malformations in the two animal species studied (see sections 4.6 and 5.3). The potential for human risk in pregnancy is unknown but cannot be excluded.
- Breastfeeding (see sections 4.6).
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).

4.4 Special warnings and precautions for use

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 antiplatelet medicines (such as acetylsalicylic acid), or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.
There is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1).

Concomitant NSAID use

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

Cardiovascular effects

Increased number of serious cardiovascular (CV) events, mainly myocardial infarction, has been found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib 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 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).
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with celecoxib after careful consideration (see section 5.1).
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

Fluid retention and oedema

Fluid retention and oedema have been observed in patients taking celecoxib. Therefore, XIBECIL 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

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 XIBECIL 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, 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 XIBECIL.

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 (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 XIBECIL 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 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 (see section 5.2).

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 (see section 4.8). 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 medicine rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome), have been reported in patients receiving celecoxib (see section 4.8). Patients with a history of sulfonamide allergy or any medicine allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). XIBECIL 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 (see section 4.5).
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).

Excipients: lactose intolerance

This medicine contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take XIBECIL.

4.5 Interaction with other medicines and other forms of interaction

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 (see section 4.4). 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 medicines 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 (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.

Ciclosporin and tacrolimus

Co-administration 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 medicines are combined.

Acetylsalicylic acid

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for CV prophylaxis.
Studies indicated 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 (see section 5.1).

Pharmacokinetic interactions

Effects of celecoxib 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 is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-dysrhythmic medicines, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with XIBECIL is initiated or increased if treatment with XIBECIL 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 subjects, co-administration of celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in Cmax of 16 % and in area under the curve (AUC) of 18 % of lithium. Therefore, patients on lithium treatment should be closely monitored when XIBECIL 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 medicines 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 (see sections 4.2 and 5.2).

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 Cmax 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Celecoxib is contraindicated in pregnancy and in women who can become pregnant (see sections 4.3 and 4.4). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see sections 4.3). 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

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 foetal 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.

Breastfeeding

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 transfer of celecoxib into breast milk. Women who take XIBECIL should not breastfeed.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions are listed by system organ class and ranked by frequency in Table 1.

Table 1. Adverse medicine reactions in celecoxib clinical trials and surveillance experience (MedDRA preferred terms)[1,2]

Frequency estimate:

Frequent

Less frequent

Not known

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
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	Hypersensitivity	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)[4], 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, dysrhythmia[4]	
Vascular disorders	Hypertension[1] (including aggravated hypertension)	Pulmonary embolism[4], flushing[4] Vasculitis[4]	
Respiratory, thoracic and mediastinal disorders	Rhinitis, cough, dyspnoea[1]	Bronchospasm[4,] Pneumonitis[4]	
Gastrointestinal disorders	Nausea[4], abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1], dysphagia[1]	Constipation, gastritis, stomatitis, Gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation, Gastrointestinal haemorrhage[4], duodenal ulcer,	

		gastric ulcer, oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, 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], medicine reaction with eosinophilia and systemic symptoms (DRESS) [4], acute generalised exanthematous pustulosis (AGEP)[4], dermatitis bullous[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], hypo-natraemia[4],Tubulointerstitial nephritis[4], nephrotic syndrome[4], glomerulonephritis minimal lesion[4]	
Reproductive system and breast disorders		Menstrual disorder[4]	Infertility female (female fertility decreased)[3]

General disorders and administration site conditions	Influenza-like illness, Oedema peripheral/fluid retention	Face oedema, chest pain[4]	
Injury, poisoning and procedural complications	Injury (accidental injury)		

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA 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 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 medicine removal due to high protein binding.

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 inhibitor (SCI). Cyclooxygenase 2 (COX-2) is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, oedema and pain. Celecoxib acts as an anti-inflammatory, analgesic and anti-pyretic agent by blocking the production of inflammatory prostanoids via COX-2 inhibition.

In vivo and ex vivo studies show that 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.

Distribution

Plasma protein binding, which is concentration independent, is about 97 % at therapeutic plasma concentrations and the medicine is not preferentially bound to erythrocytes in the blood. Dosing with food (high fat meal) delays absorption, resulting in a Tmax of about 4 hours, and increases bioavailability by about 20 %.

In the population > 65 years there is a two-fold increase in mean Cmax and AUC for celecoxib. This is a predominantly weight-related rather than age-related change, celecoxib levels being higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Therefore, elderly females tend to have slightly higher drug plasma concentrations than elderly males.

Biotransformation

Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation and in vitro and in vivo studies indicate that metabolism is mainly 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

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

pharmacokinetic parameters (AUC, Cmax, 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 the medicine crosses the blood/brain barrier.

Special population

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 medicine 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 m2) and in patients with chronic stable renal insufficiency (GFR 35 – 60 mL/min/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

At the present time the relative roles of COX-1 and COX-2 in renal physiology is incompletely understood. XIBECIL reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\alpha}$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown that XIBECIL 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules core:

Lactose Monohydrate

Croscarmellose Sodium

Sodium Lauryl Sulfate

Povidone (K-30)

Magnesium Stearate

Empty capsule shell:

Gelatin

Sodium Lauryl Sulphate

Titanium dioxide (E171)

Printing Ink (BLUE TEK SB 6018):

Shellac (E904)

Dehydrated Alcohol (E1510)

Isopropyl Alcohol

Butyl Alcohol

Propylene Glycol (E1520)

Strong Ammonia Solution (E527)

FD & C Blue # 2 Aluminium Lake (Indigo Carmine) (E132) for 100 mg capsules

Yellow Iron Oxide NF (E132) for 200 mg capsules

6.2 Incompatibilities

Not applicable.

6. Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25°C.

Store in original packaging.

6.5 Nature and contents of container

Blister Pack:

XIBECIL hard gelatin capsules are packed in Alu foil blister strips or transparent PVC/PE/PVDC - Alu blister strips, each containing 10 capsules. The capsules are placed in an outer cardboard carton.

Pack sizes: 10,30 or 60 capsules in a carton.

Bulk/Jar Pack:

XIBECIL hard gelatin capsules are packed in HDPE jars –100 capsules are packed in a HDPE container with HDPE Cap along with silica gel bag and sealed Aluminium tagger. Each jar is packed in carton along with a PIL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

XIBECIL 100: 55/3.1/0615.613

XIBECIL 200: 55/3.1/0616.614

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 July 2023

10. DATE OF REVISION OF THE TEXT