1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

LEXIB 100 mg **c**apsules

LEXIB 200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEXIB 100 mg: Each capsule contains 100 mg celecoxib

Contains sugar (lactose monohydrate 20,225 mg/capsule)

LEXIB 200 mg: Each capsule contains 200 mg celecoxib

Contains sugar (lactose monohydrate 40,45 mg/capsule)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

LEXIB 100 mg: Size '3', White to White opaque hard gelatin capsules, imprinted with 'CEL' on cap & '100 mg' on body in black ink, filled with white to off-white slug to granular powder.

LEXIB 200 mg: Size '2', White to White opaque hard gelatin capsules, imprinted with 'CEL' on cap & '200 mg' on body in black ink, filled with white to off-white slug to granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LEXIB is indicated for 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.

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4.2 Posology and method of administration

Posology

Use in adults:

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

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:

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.

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. Introduce **LEXIB** 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, 4.4 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, 4.4 and 5.2).

Paediatric population:

LEXIB is not indicated for use in children.

Method of administration

For oral use

4.3 Contraindications

Hypersensitivity to celecoxib or any other ingredient of **LEXIB** listed in section 6.1

Known sulphonamide hypersensitivity.

Active peptic ulceration or gastrointestinal (GI) bleeding.

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 animal species studied (see sections 4.6). The potential for human risk in pregnancy is unknown but cannot be excluded.

Breast-feeding.

Severe impairment of hepatic function.

Severe impairment of renal function.

Asthma, urticaria or allergic-type reactions precipitated by aspirin or non-steroidal anti-inflammatory drugs, including other cyclooxygenase 2 (COX-2) specific inhibitors.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

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).

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

Hypertension

Celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

Hepatic and renal effects

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

NSAIDs, including celecoxib, may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with celecoxib.

Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis and, hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment (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 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 medicinal products 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 drug 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 drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General

Celecoxib may mask fever and other signs of inflammation.

Use with oral anticoagulants

In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported. Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with celecoxib is initiated or celecoxib dose is changed (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

LEXIB 100 mg and 200 mg capsules contain lactose (20.25 mg and 40.45 mg, respectively). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **LEXIB**.

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 medicinal products including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics, or elderly patients) when ACE-inhibitors, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including celecoxib (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.

In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg twice daily resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg twice daily, 48 % were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood

pressure >90 mmHg or cuff diastolic blood pressure increased >10 % compared to baseline), compared to 27 % of patients treated with placebo; this difference was statistically significant.

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 medicinal products are combined.

Acetylsalicylic acid

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. 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 medicinal products

CYP2D6 inhibition

Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicinal products that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of medicinal products which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-dysrhythmic medicinal products, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.

Concomitant administration of celecoxib 200 mg twice daily resulted in 2.6-fold and 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib 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 medicinal products 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 medicinal products.

Lithium

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

Oral contraceptives

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone /35 micrograms ethinylestradiol).

Glibenclamide/tolbutamide

Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.

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

Ketoconazole and antacids

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity, including malformations (see sections 4.3). Inhibition of prostaglandin syntheses 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. 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.

Breast-feeding

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

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 celecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The following side effects have been reported in patients on **LEXIB** treatment.

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

Table 1. Adverse Drug Reactions

MedDRA system organ class	Frequency	Undesirable effect
Infections and infestations	Frequent	Sinusitis, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Less frequent	Anemia
		Leucopenia, thrombocytopenia
		Pancytopenia
Immune system disorders	Frequent	Allergy aggravated (hypersensitivity)
	Less frequent	Anaphylactic shock, anaphylaxis(anaphylactic reaction)
Metabolism and nutrition disorders	Less frequent	Hyperkaelemia
Psychiatric disorders	Frequent	Insomnia
	Less frequent	Anxiety, depression, tiredness
		Confusion (confusional state), hallucinations
Nervous system disorders	Frequent	Dizziness, hypertonia, headache
	Less frequent	Cerebral infarction, paraesthesia, somnolence
		Ataxia, taste alteration
		Fatal intracranial haemorrhage, meningitis aseptic, aggravated epilepsy, ageusia, anosmia
Eye disorders	Less frequent	Blurred vision, conjunctivitis
		Ocular haemorrhage
		Retinal artery occlusion, retinal vein occlusion
Ear and labyrinth disorders	Less frequent	Tinnitus, hypoacusis
Cardiac disorders	Frequent	Myocardial infarction
	Less frequent	Heart failure, palpitations, tachycardia
		Arrhythmia
Vascular disorders	Frequent	Hypertension (including aggravated hypertension)
	Less frequent	Pulmonary embolism, flushing
		Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis, rhinitis, coughing (cough), dyspnoea
	Less frequent	Bronchospasm
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia
	Less frequent	Constipation, gastritis, stomatitis, aggravation of gastrointestinal inflammation, eructation
		Gastrointestinal haemorrhage, duodenal, gastric, oesophageal, intestinal, and colonic ulceration, intestinal perforation, oesophagitis, melaena, pancreatitis, colitis/colitis aggravated
Hepatobiliary disorders	Less frequent	Abnormal hepatic function, elevation of hepatic enzymes (including increased SGOT and SGPT)
		Hepatitis

		Hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis[4] (some with fatal outcome), liver necrosis, cholestasis, cholestatic hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus (includes pruritus generalised)
	Less frequent	Urticaria, ecchymosis
		Angioedema, alopecia, photosensitivity
		Exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) or hypersensitivity syndrome, acute generalised exanthematous pustulosis (AGEP), bullous eruption (dermatitis bullous)
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia
	Less frequent	Leg cramps
		Myositis
Renal and urinary disorders	Less frequent	Increased creatinine, BUN increased
		Acute renal failure, hyponatraemia
		Interstitial nephritis, nephrotic syndrome, minimal change disease
Reproductive system and breast disorders	Less frequent	Menstrual disorder NOS
	Frequency unknown	Female fertility decreased
General disorders and administration site conditions	Frequent	Flu-like symptoms (influenze-like illness), peripheral oedema/ fluid retention
	Less frequent	Face oedema, chest pain
Injury, poisoning and procedural conditions	Frequent	Accidental injury (injury)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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 and, if necessary, the institution of symptomatic treatment. Dialysis is unlikely to be an efficient method of medicinal product removal due to high protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic medicines, NSAIDs, Coxibs, ATC code: M01AH01.

Mechanism of action

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

Pharmacodynamic effects

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2 have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in humans but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide antibiotics).

A dose-dependent effect on TxB2 formation has been observed after high doses of celecoxib. However, in healthy subjects, in small multiple dose studies with 600 mg BID (three times the highest recommended dose) celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.

5.2 Pharmacokinetic properties

Absorption

Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour.

Distribution

Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes.

Biotransformation

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma i.e., a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Elimination

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

Special populations

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism.

Patients who are known or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution (see section 4.2).

No clinically significant differences were found in PK parameters of celecoxib between elderly African-Americans and Caucasians.

The plasma concentration of celecoxib is approximately 100% increased in elderly women (> 65 years).

Hepatic impairment:

Compared to subjects with normal hepatic function, patients with mild hepatic impairment had a mean increase in C_{max} of 53% and in AUC of 26% of celecoxib. The corresponding values in patients with moderate hepatic impairment were 41% and 146% respectively. The metabolic capacity in patients with mild to moderate impairment was best correlated to their albumin values. Treatment should be initiated at half the recommended dose in patients with moderate liver impairment (with serum albumin 25-35 g/L). Patients with severe hepatic impairment (serum albumin < 25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

Renal impairment:

There is little experience of celecoxib in renal impairment. The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus caution is advised when treating patients with renal impairment. Severe renal impairment is contraindicated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content:

croscarmellose sodium

lactose monohydrate

magnesium stearate

povidone

sodium lauryl sulphate

Capsule shells:

gelatin

sodium lauryl sulphate

titanium dioxide

Printing ink:

shellac

dehydrated alcohol

isopropyl alcohol

butyl alcohol

propylene glycol

ammonia solution concentrated

black iron oxide

potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25°C.

Store the capsules in the original blisters and keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

Lexib 100 mg capsules Blister pack with PVC/PE laminate & Aluminum lid foil with outer carton in packs of 28, 30, 56, 60, 100

Lexib 200 mg capsules Blister pack with PVC/PE laminate & Aluminum lid foil with outer carton in packs of 28, 30, 56, 60, 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Overport, Durban

4091

8 REGISTRATION NUMBER(S)

LEXIB 100 – 54/3.1/0039

LEXIB 200 – 54/3.1/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT