APPROVED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

CELEBREX® 100 Capsules

CELEBREX® 200 Capsules

COMPOSITION:

Each 100 mg capsule contains 100 mg celecoxib

Each 200 mg capsule contains 200 mg celecoxib

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Antirheumatics (anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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).

Pharmacokinetic properties:

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, which is concentration independent, is about 97 % at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes in

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

In the population > 65 years there is a two-fold increase in mean C_{max} and AUC for celecoxib. This is a predominantly weight-related rather than age-related change, celecoxib levels 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.

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 drug. The main metabolites found in the circulation have no detectable COX-1 or COX-2 inhibitory activity.

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, C_{max}, elimination half-life) is about 30 %. The mean steady state volume of distribution is about 500 l/70 kg in young healthy adults after a single 200 mg dose, indicating wide distribution of celecoxib into the tissues. Pre-clinical studies indicate that the drug crosses the blood/brain barrier.

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 drug 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:

At the present time the relative roles of COX-1 and COX-2 in renal physiology is incompletely understood. CELEBREX reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\propto}$ (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 CELEBREX 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.

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.

CONTRAINDICATIONS:

Hypersensitivity to CELEBREX or any other ingredient of the product.

Known sulphonamide hypersensitivity.

Severe impairment of hepatic function.

Severe impairment of renal function.

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

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).

WARNINGS AND SPECIAL PRECAUTIONS:

CELEBREX may predispose to cardiovascular events, cerebrovascular events, gastrointestinal

events or cutaneous reactions which may be fatal.

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

Cardiovascular effects:

There is insufficient data to assess cardiovascular safety beyond one year of continuous treatment. CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment. Caution is advised when CELEBREX is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms.

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Gastrointestinal (GI) effects:

Upper gastrointestinal perforations, ulcers or bleeds have occurred in patients treated with celecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Most spontaneous reports of fatal gastrointestinal events have been in elderly or debilitated patients.

Serious skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of CELEBREX. 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. CELEBREX should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Celecoxib contains a sulphonamide moiety. In clinical trials CELEBREX did not induce bronchospasm in patients with asthma. However, CELEBREX has not been evaluated in patients in whom attacks of

asthma, urticaria or acute rhinitis have been precipitated by aspirin or non-steroidal anti-inflammatory agents. Use in such patients should be avoided until further information is available.

Fluid retention and oedema:

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking celecoxib, therefore CELEBREX should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Renal effects:

Renal function should be closely monitored in patients with advanced renal disease who are administered CELEBREX.

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

Hepatic effects:

A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX.

Anaphylactoid reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to CELEBREX (see CONTRAINDICATIONS).

General:

By reducing inflammation, CELEBREX may diminish the utility of diagnostic signs, such as fever, in detecting infections.

Use with warfarin or similar agents:

In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulant activity should be monitored after initiating treatment with celecoxib or changing the dose.

Effects on ability to drive and use machines:

The effect of CELEBREX on ability to drive or use machinery has not been studied, but based on its pharmacodynamic properties and overall safety profile it is unlikely to have an effect.

INTERACTIONS:

General:

Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolised by P450 CYP2D6.

ACE-inhibitors:

Inhibition of prostaglandins may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

Aspirin:

CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thromboembolic events associated with CELEBREX.

Fluconazole:

Concomitant administration of fluconazole at 200 mg qd resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 CYP2C9 by fluconazole. CELEBREX should be introduced at the lowest recommended dose in patients receiving the CYP2C9 inhibitor fluconazole.

Diuretics:

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.

Lithium:

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17 % in subjects receiving lithium 450 mg bid with CELEBREX 200 mg bid as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate:

In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Other:

In specific studies in healthy volunteers with other agents metabolised by CYP2C9, CELEBREX was found to produce no clinically significant pharmacokinetic interaction with phenytoin or tolbutamide.

Oral contraceptives:

In an interaction study, CELEBREX had no clinically relevant effects on the pharmacokinetics of a prototype combination oral contraceptive (1 mg norethinderone/0,035 mg ethinyl estradiol).

Warfarin:

In patients on concurrent therapy with warfarin, increases in prothrombin time (INR) have been reported (see WARNINGS AND SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION:

CELEBREX, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during pregnancy.

Limited data indicate that CELEBREX is excreted in breast milk and therefore should not be used during lactation.

DOSAGE AND DIRECTIONS FOR USE:

As the cardiovascular risks of CELEBREX 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.

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 CELEBREX at the lowest recommended dose in patients with moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment (see CONTRAINDICATIONS).

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 CONTRAINDICATIONS).

Children:

CELEBREX has not been studied in subjects under 18 years old.

SIDE EFFECTS:

The following side effects have been reported in patients on CELEBREX treatment. Incidence rates are categorised as follows: Common (> 1/100 and < 1/10) (> 1 % and < 10 %), Uncommon (> 1/1 000 and < 1/100) (> 0,1 % and < 1 %), Rare (> 1/10 000 and < 1/1 000) (> 0,01 % and < 0,1 %).

System organ class	**Frequency**	**Undesirable effects**
Immune system	Common	Allergy aggravated
	Rare	Angioedema
Psychiatric	Common	Insomnia
	Rare	Confusion
Nervous system	Common	Dizziness Hypertonia
Cardiac	Common	Peripheral oedema
	Uncommon	Aggravated hypertension Arrhythmia Hypertension Palpitations Tachycardia
	Rare	Congestive heart failure
Respiratory, thoracic and mediastinal	Common	Bronchitis Coughing Pharyngitis Rhinitis Sinusitis Upper respiratory tract infection
Gastrointestinal	Common	Abdominal pain Diarrhoea Dyspepsia Flatulence Tooth disorder
	Uncommon	Vomiting

	Rare	Pancreatitis Gastric ulcer Duodenal ulcer Oesophageal ulceration Intestinal perforation
Skin and subcutaneous tissue	Common	Rash Pruritus
	Uncommon	Alopecia Urticaria
	Rare	Bullous eruptions
Renal and urinary	Common	Urinary tract infection
General disorders and administration site conditions	Common	'Flu-like symptoms
Injury, poisoning and procedural complications	Common	Accidental injury
Blood and the lymphatic system	Uncommon	Anaemia Ecchymosis Thrombocytopenia
Psychiatric	Uncommon	Anxiety Somnolence
Eye	Uncommon	Blurred vision
Ear and labyrinth	Uncommon	Tinnitus
Vascular	Uncommon	Flushing
Hepatobiliary	Rare	Elevation of hepatic enzymes

Post-marketing experience:

Reactions from post-marketing experience include the following:

Immune system: Anaphylaxis

Psychiatric: Hallucinations

Nervous system disorders: Ageusia, anosmia, aseptic meningitis

Vascular: Vasculitis

Gastrointestinal: Gastrointestinal haemorrhage

Hepatobiliary: Hepatitis, liver failure

Renal and urinary: Acute renal failure, interstitial nephritis

Skin and subcutaneous tissue: Photosensitivity reaction, skin exfoliation (including erythema multiforme and Stevens-Johnson syndrome)

Cardiac: Myocardial infarction, cardiovascular thrombotic events

Neurologic: Cerebrovascular incident (stroke)

Reproductive system and breast disorders: Menstrual disorder

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 drug removal.

IDENTIFICATION:

CELEBREX 100: Opaque, white to off-white, hard gelatine capsule with a blue band marked 7767 and 100, containing a white to off-white granulation.

CELEBREX 200: Opaque, white to off-white, hard gelatine capsule with a gold band marked 7767 and 200, containing a white to off-white granulation.

PRESENTATION:

CELEBREX 100: Blister packs of 60 capsules

CELEBREX 200: Blister packs of 10, 15 or 30 capsules

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep out of reach of children.

REGISTRATION NUMBERS:

CELEBREX 100: 33/3.1/0332

CELEBREX 200: 33/3.1/0333

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

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NAMIBIA: S2

CELEBREX 100 – Reg. No.: 04/3.1/0721

CELEBREX 200 – Reg. No.: 04/3.1/0722

BOTSWANA: S2

CELEBREX 100 – Reg. No.: BOT0801379

CELEBREX 200 – Reg. No.: BOT0801377