

SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

CELEBREX® 100 capsules

CELEBREX® 200 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg capsule contains 100 mg celecoxib.

Each 200 mg capsule contains 200 mg celecoxib.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each 100 mg capsule contains 149,7 mg lactose monohydrate.

Each 200 mg capsule contains 49,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

CELEBREX 100: Hard gelatine capsule (containing white to off-white granulation). White, opaque body with blue ink band containing in white '100'; white, opaque cap with blue ink band containing in white '7767'. Each blue ink band nearly, but not completely circumscribes the capsule.

CELEBREX 200: Hard gelatine capsule (containing white to off-white granulation). White, opaque body with gold ink band containing in white '200'; white, opaque cap with gold ink band containing in white '7767'. Each gold ink band nearly, but not completely circumscribes the capsule.

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 CELEBREX 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 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 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 CELEBREX 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).

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).

Paediatric population

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to celecoxib or to any of the excipients of CELEBREX.
- 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 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 in the setting of coronary artery bypass surgery (CABG).

4.4 Special warnings and precautions for use

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. Medical practitioners 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 CELEBREX. 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 NSAIDs. Use in such patients should be avoided until further information is available.

Fluid retention and oedema

As with other medicines known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking CELEBREX, 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 section 4.3).

General

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

Use with warfarin or similar medicines

In patients on concurrent therapy with warfarin or similar medicines, 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 CELEBREX or changing the dose.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

General

CELEBREX metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of CELEBREX with medicines 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* medicine interaction with medicines 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 once daily 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 twice daily with CELEBREX 200 mg twice daily 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 medicines

In specific studies in healthy volunteers with other medicines 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 norethindrone/0,035 mg ethinyl estradiol).

Warfarin

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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

4.7 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following side effects have been reported in patients on CELEBREX treatment. Incidence rates are categorised as follows: Common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ and $< 1/1\ 000$).

MedDRA System Organ Class	Frequency	Undesirable effects
<i>Blood and lymphatic system disorders</i>	Uncommon	Anaemia, ecchymosis, thrombocytopenia
<i>Immune system disorders</i>	Common	Allergy aggravated
	Rare	Angioedema
<i>Psychiatric disorders</i>	Common	Insomnia
	Uncommon	Anxiety, somnolence
	Rare	Confusion
<i>Nervous system disorders</i>	Common	Dizziness, hypertonia
<i>Eye disorders</i>	Uncommon	Blurred vision
<i>Ear and labyrinth disorders</i>	Uncommon	Tinnitus
<i>Cardiac disorders</i>	Common	Peripheral oedema
	Uncommon	Aggravated hypertension, arrhythmia, hypertension, palpitations, tachycardia
	Rare	Congestive heart failure
<i>Vascular disorders</i>	Uncommon	Flushing
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	Bronchitis, coughing, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection
<i>Gastrointestinal disorders</i>	Common	Abdominal pain, diarrhoea, dyspepsia, flatulence, tooth disorder
	Uncommon	Vomiting

	Rare	Pancreatitis, gastric ulcer, duodenal ulcer, oesophageal ulceration, intestinal perforation
<i>Hepatobiliary disorders</i>	Rare	Elevation of hepatic enzymes
<i>Skin and subcutaneous tissue disorders</i>	Common	Rash, pruritus
	Uncommon	Alopecia, urticaria
	Rare	Bullous eruptions
<i>Renal and urinary disorders</i>	Common	Urinary tract infection
<i>General disorders and administration site conditions</i>	Common	'Flu-like symptoms
<i>Injury, poisoning and procedural complications</i>	Common	Accidental injury

Post-marketing experience

Reactions from post-marketing experience include the following:

MedDRA System Organ Class	Undesirable effects
<i>Immune system disorders</i>	Anaphylaxis
<i>Psychiatric disorders</i>	Hallucinations
<i>Nervous system disorders</i>	Ageusia, anosmia, aseptic meningitis, cerebrovascular incident (stroke)
<i>Cardiac disorders</i>	Myocardial infarction, cardiovascular thrombotic events
<i>Vascular disorders</i>	Vasculitis
<i>Gastrointestinal disorders</i>	Gastrointestinal haemorrhage
<i>Hepatobiliary disorders</i>	Hepatitis, liver failure
<i>Skin and subcutaneous tissue disorders</i>	Photosensitivity reaction, skin exfoliation (including erythema multiforme and Stevens-Johnson syndrome)
<i>Renal and urinary disorders</i>	Acute renal failure, interstitial nephritis
<i>Reproductive system and breast disorders</i>	Menstrual disorder

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions 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 and class: A 3.1 Antirheumatics (anti-inflammatory agents)

Mechanism of action

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

Distribution

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

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, 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 medicine crosses the blood/brain barrier.

Linearity/non-linearity:

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

Special populations

Elderly

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.

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 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. Celecoxib reduces the urinary excretion of PGE₂ and 6-keto-PGF_{1α} (a prostacyclin metabolite) but leaves serum thromboxane B₂ (TXB₂) and urinary excretion of 11-dehydro-TXB₂, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown that celecoxib 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 content

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Povidone

Sodium lauryl sulphate

Capsule shells

Gelatine

Titanium dioxide

Printing ink

Butyl alcohol (E1013200)

Dehydrated alcohol (E1034800)

FD&C Blue #2 Aluminium Lake (E132) (100 mg)

Isopropyl alcohol

Propylene glycol

Shellac

Strong ammonia solution

Yellow ferric oxide (E172) (200 mg)

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

CELEBEX 100: Blister packs of 60 capsules.

CELEBEX 200: Blister packs of 10, 15 or 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

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Manufacturer: Pfizer Pharmaceuticals LLC, Vega Baja, Puerto Rico; Neolpharma, Inc., Caguas, Puerto Rico

8. REGISTRATION NUMBERS

CELEBREX 100: 33/3.1/0332

CELEBREX 200: 33/3.1/0333

9. DATE OF FIRST AUTHORISATION

28 January 2000

10. DATE OF REVISION OF THE TEXT

11 December 2008

BOTSWANA: S2

CELEBREX 100 – Reg. No.: BOT0801379

CELEBREX 200 – Reg. No.: BOT0801377

NAMIBIA: NS2

CELEBREX 100 – Reg. No.: 04/3.1/0721

CELEBREX 200 – Reg. No.: 04/3.1/0722