PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

CELECOXIB UNICORN® 100 (capsules)

CELECOXIB UNICORN® 200 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELECOXIB UNICORN 100 capsule contains 100 mg celecoxib.

Each CELECOXIB UNICORN 200 capsule contains 200 mg celecoxib.

Excipient with known effect:

Each CELECOXIB UNICORN 100 capsule contains sugar (7 mg lactose monohydrate).

Each CELECOXIB UNICORN 200 capsule contains sugar (14 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CELECOXIB UNICORN 100 mg: Blue capsule with white body, which contains white to slightly yellowish pellets.

CELECOXIB UNICORN 200 mg: Orange capsule with white body, which contains white to slightly yellowish pellets.

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

Posology:

Osteoarthritis: The recommended daily dose is 200 mg taken as a single 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.

Post dental surgery pain: 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 (older than 65 years): 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 CELECOXIB UNICORN at half the 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).

CYP2C9 poor metabolisers:

Patients who are known or suspected to be CYP2C9 poor metabolisers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered CELECOXIB UNICORN with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose (see section 5.2).

Paediatric population: CELECOXIB UNICORN has not been studied in patients under 18 years old.

Method of administration:

Oral use.

CELECOXIB UNICORN may be taken with or without food.

4.3 Contraindications

- Known hypersensitivity to celecoxib, or to any of the ingredients of CELECOXIB UNICORN listed in section 6.1.
- Known sulphonamide hypersensitivity.
- Active peptic ulceration or gastrointestinal bleeding.
- Inflammatory bowel disease.
- Severe impairment of hepatic function (Child Pugh score ≥ 10).
- Severe impairment of renal function (estimated creatinine clearance < 30 ml/min).
- Congestive heart failure.
- Asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions precipitated by aspirin or non-steroidal anti-inflammatory medicines 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).
- In women of childbearing potential unless using effective contraceptive methods.
- Pregnancy - risk of foetal renal dysfunction (see section 4.6).
- Lactation.

4.4 Special warnings and precautions for use

CELECOXIB UNICORN may predispose to cardiovascular events, cerebrovascular events, gastro-intestinal events or cutaneous reactions which may be fatal.

The safety and efficacy of CELECOXIB UNICORN have not been established for treatment exceeding 12 weeks in osteoarthritis and 24 weeks in rheumatoid arthritis.

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 as in CELECOXIB UNICORN. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs (Non-steroidal anti-inflammatory drugs); 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 as in CELECOXIB UNICORN (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.

Concomitant NSAID use:

The concomitant use of celecoxib as in CELECOXIB UNICORN and a non-aspirin NSAID should be avoided.

Cardiovascular effects:

CELECOXIB UNICORN may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. There is insufficient data to assess cardiovascular safety beyond one year of continuous treatment. 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 section 4.2, 4.3 and 4.8).

Caution is advised when CELECOXIB UNICORN is prescribed to patients with cardiovascular risk factors e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking. Medical practitioners and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. CELECOXIB UNICORN is not a substitute for aspirin for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Fluid retention and oedema:

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking celecoxib, therefore CELECOXIB UNICORN 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 as in CELECOXIB UNICORN 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 and throughout the course of therapy.

Hepatic and renal effects:

Renal function should be closely monitored in patients with advanced renal disease who receive CELECOXIB UNICORN. Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with CELECOXIB UNICORN.

NSAIDs, including celecoxib, may cause renal toxicity. 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. Such patients should be carefully monitored while receiving treatment with CELECOXIB UNICORN.

The use of NSAIDs, including celecoxib, is also associated with a risk of renal tubular acidosis (RTA) and hypokalaemia.

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 severe hepatic reaction while on therapy with CELECOXIB UNICORN.

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.

If during treatment, patients deteriorate in any of the organ system functions (hepatic or renal) described above, appropriate measures should be taken and discontinuation of CELECOXIB UNICORN therapy should be considered.

Poor metabolisers of CYP2C9 substrates:

Patients known to be CYP2C9 poor metabolisers should be treated with caution.

In adult patients who are known or suspected to be poor CYP2C9 metabolisers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.
In patients with Juvenile Rheumatoid Arthritis who are known or suspected to be poor CYP2C9 metabolisers, consider using alternative treatments.

CYP2D6 substrates:

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolised by CYP2D6 (e.g. atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs. Patients known to be CYP2C9 poor metabolisers should be treated with caution.

Skin and systemic hypersensitivity reactions*:*

Anaphylactic reactions have occurred in patients exposed to celecoxib as in CELECOXIB UNICORN (see section 4.3).
Serious skin reactions, some fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of celecoxib as in CELECOXIB UNICORN (see section 4.8). Patients appear to be at highest risk for these events early in the course of therapy; the onset of the event occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (including anaphylaxis, angioedema and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), or hypersensitivity syndrome), have been reported in patients receiving celecoxib as in CELECOXIB UNICORN. Patients with a history of sulfonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. CELECOXIB UNICORN should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

General:

By reducing inflammation, CELECOXIB UNICORN 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, 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 as in CELECOXIB UNICORN is initiated or CELECOXIB UNICORN 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 UNICORN with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipient:

CELECOXIB UNICORN contains lactose monohydrate. Patients with the rare hereditary problems of galactose intolerance] total lactase deficiency, glucose-galactose malabsorption should not take CELECOXIB UNICORN.

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 UNICORN 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

UNICORN is initiated or the dose of CELECOXIB UNICORN is changed (see section 4.4). Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly and in patients receiving celecoxib as in CELECOXIB UNICORN 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 UNICORN (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.

Aspirin:

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

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 UNICORN and any of these medicines are combined.

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-arrhythmic medicines, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with CELECOXIB UNICORN is initiated or increased if treatment with CELECOXIB UNICORN 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.

CYP2C9 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 as in CELECOXIB UNICORN 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:

Patients on lithium treatment should be closely monitored when CELECOXIB UNICORN is introduced or withdrawn.

Oral contraceptives:

In an interaction study, celecoxib as in CELECOXIB UNICORN had no clinically relevant effects on the pharmacokinetics of a prototype combination oral contraceptive (1 mg norethindrone/0,035 mg ethinyl estradiol).

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).

Fluconazole:

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

CYP2C9 inhibitors and inducers:

Since celecoxib as in CELECOXIB UNICORN 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 UNICORN.

Ketoconazole and antacids:

Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib as in CELECOXIB UNICORN.

Diuretics:

NSAIDs as in CELECOXIB UNICORN can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

4.6 Fertility, pregnancy and lactation

Pregnancy:

CELECOXIB UNICORN inhibit prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during pregnancy (see section 4.3).

During the second or third trimester of pregnancy, NSAIDs including CELECOXIB UNICORN 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. CELECOXIB UNICORN 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 UNICORN should be discontinued.

Breastfeeding:

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

Fertility:

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including CELECOXIB UNICORN, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including CELECOXIB UNICORN, in women who have difficulties conceiving or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Infections and infestations:

***Frequent*:** Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection.

Blood and lymphatic system disorders:

***Less frequent*:** Anaemia, ecchymosis, thrombocytopenia, leukopenia, pancytopenia.

Immune system disorders:

Frequent: Allergy aggravated.

Less frequent*:* Angioedema, anaphylactic shock, anaphylactic reaction, hypersensitivity.

Metabolism and nutrition disorders:

Less frequent: Hyperkalaemia.

Psychiatric disorders:

Frequent: Insomnia.

Less frequent: Anxiety, confusional state, depression, hallucinations, fatigue.

Nervous system disorders:

Frequent: Dizziness, hypertonia, headache.

Less frequent: Cerebral infarction, paraesthesia, ataxia, dysgeusia, somnolence.

***Frequency unknown*:** Haemorrhage intracranial (including fatal intracranial haemorrhage), meningitis aseptic, epilepsy (including aggravated epilepsy), ageusia, anosmia, cerebrovascular incident (stroke).

Eye disorders:

Less frequent: Blurred vision, conjunctivitis, eye haemorrhage, retinal artery occlusion, retinal vein occlusion.

Ear and labyrinth disorders:

Less frequent: Tinnitus, hypoacusis.

Cardiac disorders:

Frequent: Peripheral oedema, myocardial infarction.

Less frequent: Aggravated hypertension, dysrhythmia, hypertension, palpitations, tachycardia, congestive heart failure.

Frequency unknown: Cardiovascular thrombotic events.

Vascular disorders:

Frequent: Hypertension (including aggravated hypertension)

Less frequent: Pulmonary embolism, flushing, vasculitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Rhinitis, cough, dyspnoea

Less frequent: Bronchospasm, pneumonitis, bronchitis, coughing.

Frequency unknown: *Pulmonary embolism.*

Gastrointestinal disorders:

Frequent: Abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, dysphagia, vomiting, tooth disorder.

Less frequent: Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation, gastrointestinal haemorrhage, pancreatitis, gastric ulcer, duodenal ulcer, oesophageal ulceration, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, colitis.

Hepatobiliary disorders:

Less frequent: Abnormal hepatic function, increased hepatic enzyme (including increased SGOT and SGPT), hepatitis, hepatic failure (sometimes fatal or requiring liver transplant), hepatitis fulminant, hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus (includes pruritus generalised).

Less frequent: Alopecia, urticaria, ecchymosis, angioedema, photo-sensitivity, dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalised Exanthematous Pustulosis (AGEP), dermatitis bullous.

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia.

Less frequent: Muscle spasms (leg cramps), myositis.

Renal and urinary disorders:

Less Frequent: Urinary tract infection, blood creatinine increased, blood urea increased (BUN), renal failure acute, hyponatraemia, tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion.

Reproductive system and breast disorders:

Less Frequent: Menstrual disorder.

Frequency unknown: Infertility female (female fertility decreased).

General disorders and administration site conditions:

Frequent: Influenza-like illness, oedema peripheral/fluid retention.

Less frequent: Face oedema, chest pain.

Injury and poisoning:

Frequent: Accidental injury.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicines is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via the website: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

In the event of suspected overdose, appropriate supportive medical care should be provided. Dialysis is unlikely to be an efficient method of removal.

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Pharmacodynamic properties

Category and class: A3.1 Antirheumatics (anti-inflammatory agents)

Mechanism of action:

Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200 to 400 mg daily).

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 antipyretic 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 well absorbed, reaching peak plasma concentrations after approximately 2 to 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:

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.

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 drug. The main metabolites found in the circulation have no detectable COX-1 or COX-2 inhibitory activity. 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 metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution (see section 4.2).

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 to 12 hours and the rate of clearance about 500 m[ℓ]L /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.

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 medicine 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 the 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 relevant roles of COX-1 and COX-2 in renal physiology are incompletely understood. Celecoxib 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 celecoxib produces no decrease in GFR in the elderly or those with chronic renal insufficiency. These studies have shown transient reductions in fractional excretion of sodium.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carrageenan, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium laurilsulfate.

Body composition: gelatine; titanium dioxide.

CELECOXIB UNICORN 100 mg cap composition: gelatine, indigo-carmine FD&C Blue 2, titanium dioxide.

CELECOXIB UNICORN 200 mg cap composition: gelatine, red iron oxide, titanium dioxide, yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Celecoxib capsules 100 and 200 mg are packed into Al/PVC/TE/PVDC blisters.

Pack sizes: CELECOXIB UNICORN 100 and CELECOXIB UNICORN 200 are packed in 10's, 30's and 60's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER(S)

CELECOXIB UNICORN® 100: 46/3.1/0702

CELECOXIB UNICORN® 200: 46/3.1/0703

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2017

10. DATE OF REVISION OF THE TEXT

23 June 2023

[1]Company Reg. No.: 1990/001979/07