PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

COXLEON® 100 (capsules)

COXLEON® 200 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COXLEON 100 capsule contains 100 mg celecoxib.

Each COXLEON 200 capsule contains 200 mg celecoxib.

Excipient with known effect:

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

COXLEON 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:

As the cardiovascular risks of COXLEON 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 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.

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 COXLEON 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).

Children: COXLEON has not been studied in patients under 18 years old.

Method of administration:

Oral use.

4.3 Contraindications

- Known hypersensitivity to celecoxib, or to any of the ingredients of COXLEON.
- 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).
- Pregnancy and in women of childbearing potential unless using effective contraceptive methods.
- Pregnancy - risk of foetal renal dysfunction (see section 4.4 and 4.6).
- Lactation.

4.4 Special warnings and precautions for use

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

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

During 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

Gastrointestinal (GI) effects:

Upper and lower gastrointestinal complications (perforations, ulcers or bleedings [PUBs]), some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or antiplatelet drugs

(such as acetylsalicylic acid) or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials.

Concomitant NSAID use:

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

Cardiovascular effects:

COXLEON 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 COXLEON is prescribed to patients with cardiovascular risk factors e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking. General practitioners and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. COXLEON 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 COXLEON 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:

As with all NSAIDS, 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 and throughout the course of therapy.

Hepatic and renal effects:

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

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 COXLEON.

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 COXLEON.

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 COXLEON 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 COXLEON (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 COXLEON (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 COXLEON. Patients with a history of sulfonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions.

COXLEON should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

General:

By reducing inflammation, COXLEON 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 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 COXLEON with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipient:

COXLEON contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take COXLEON.

COXLEON contains lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus.

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 and in patients receiving celecoxib concurrently with warfarin, some of them fatal.

Anti-hypertensives:

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

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

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for CV prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to the use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.

Ciclosporin and tacrolimus:

Co-administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when celecoxib and any of these medicines are combined.

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 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.

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 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 COXLEON is introduced or withdrawn.

Oral contraceptives:

In an interaction study, celecoxib as in COXLEON 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. COXLEON should be introduced at the lowest recommended dose in patients receiving the CYP2C9 inhibitor fluconazole.

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.

Diuretics:

NSAIDs 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:

COXLEON as with other medicines inhibiting 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 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 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.

Lactation:

Limited data indicate that COXLEON 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 COXLEON, 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 COXLEON, 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 COXLEON 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, hypersensitivity.

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

Metabolism and nutrition disorders:

Less frequent: Hyperkalaemia.

Psychiatric disorders:

Frequent: Insomnia.

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

Nervous system disorders:

Frequent: Dizziness, hypertonia, headache.

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

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

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, cardiac failure.

Frequency unknown: Cardiovascular thrombotic events, arrhythmia.

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, pharyngitis, sinusitis, upper respiratory tract infection.

Gastrointestinal disorders:

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

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 patientsafety.sacg@novartis.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**.**

Pharmacological classification: A3.1 Antirheumatics (anti-inflammatory agents)

5.1 Pharmacodynamic properties

Pharmacodynamic properties

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.

In the population > 65 years there is a two-fold increase in mean C_{max} and AUC for celecoxib. This is 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.

Elimination:

Metabolism:

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.

Excretion:

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 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 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.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Body composition: gelatine; titanium dioxide.

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

COXLEON 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: COXLEON 100 and COXLEON 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)

COXLEON® 100: 46/3.1/0704.702

COXLEON® 200: 46/3.1/0705.703

9. DATE OF FIRST AUTHORISATION

02 June 2017

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Coxleon 100	S2	BOT1803353/A/B/C
	Coxleon 200	S2	BOT1803354/A/B/C
Namibia	Coxleon 100	NS2	15/3.1/0034
	Coxleon 200	NS2	15/3.1/0035
Zambia	Coxleon 100	POM	039/084
	Coxleon 200	POM	039/085

ATC Code: M01AH01 – Coxibs

Name and address of manufacturer:

Lek Pharmaceuticals, d.d.

Verovškova 57

1526 Ljubljana

Slovenia

10. DATE OF REVISION OF THE TEXT

06 May 2021

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