Clean Proposed Professional Information (PI)

for Medicines for Human Use

COXITEC 7,5 mg (Tablets)

COXITEC 15 mg (Tablets)

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

COXITEC 7,5 mg (Tablets)

COXITEC 15 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

COXITEC 7,5 mg: Each tablet contains meloxicam 7.5 mg

COXITEC 15 mg: Each tablet contains meloxicam 15 mg

Each **COXITEC** tablet contains 23,5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

COXITEC 7,5 mg:

Light yellow, circular, biconvex uncoated tablets with “7.5” debossed on one side and “G14” on the other side.

COXITEC 15 mg

Light yellow, oval, biconvex uncoated tablets with “15” debossed on one side and “G14” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COXITEC tablets are indicated for the symptomatic treatment of:

- Rheumatoid arthritis
- Painful osteoarthritis
- Ankylosing spondylitis
- Episodes of acute sciatica

4.2 Posology and method of administration

Posology

As the potential for adverse reactions increases with dose and duration of exposure, use the lowest effective dose for the shortest possible duration of treatment

Adults:

The maximum daily dose of **COXITEC** is 15 mg.

Acute sciatica: 7.5 mg once daily. If there is no improvement the dose can be increased to 15 mg a day.

Ankylosing spondylitis: 15 mg once daily. According to the therapeutic response, the dose may be reduced to 7,5 mg/day

Osteoarthritis: 7.5 mg once daily. Increase to 15 mg if necessary.

Rheumatoid arthritis: 15 mg once daily. Reduce dose if possible to 7,5 mg/day (provided therapeutic response is maintained).

Special populations

Elderly patients and patients with increased risks for adverse reactions (see section 5.2):

In patients with an increased risk of adverse reactions, e.g. the elderly, a history of gastrointestinal disease or risk factors for cardiovascular disease, treatment should be started at the dose of 7,5 mg/day (see section 4.4).

Renal impairment

The dose of **COXITEC** tablets in patients with end stage renal disease on haemodialysis should not be greater than 7.5 mg/day. In non-dialysed patients with severe renal impairment **COXITEC** is contraindicated (see section 4.3). ~~(~~No dosage reduction is necessary in patients with mild to moderate renal impairment~~)~~.

Paediatric Population

Safety and efficacy in children under the age of 18 years has not been established.

Method of administration

For oral administration.

The tablet should be taken with a glass of water and together with a meal.

4.3 Contraindications

- Hypersensitivity to **COXITEC** or to any of the excipients listed in section 6.1.
- Patients in whom attacks of asthma, urticaria, nasal polyps or acute rhinitis are precipitated by acetylsalicylic acid/aspirin or by other non-steroidal anti-inflammatory agents because of a potential cross-sensitivity.
- Active peptic ulcer disease.
- Severe hepatic impairment
- Severe non dialysed renal impairment
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- History of gastrointestinal bleeding or perforation (PUBs) related to previous NSAIDs, including **COXITEC.**
- Active or history of recurrent gastrointestinal ulcer/haemorrhage/perforations.

- Pregnancy (see section 4.6).
- Active inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- Overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- Peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery
- Use in children under 18 years of age.

4.4 Special warnings and precautions for use

COXITEC may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

Gastrointestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The consequences of such events are generally more serious in the elderly.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of **COXITEC** tablets, in patients with a history of ulcers, and the elderly. **COXITEC** should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see section 4.3).

Patients with a history of gastrointestinal disease should be monitored very carefully while on **COXITEC** and therapy should be discontinued if any ulceration or bleeding occurs.

When gastrointestinal bleeding or ulceration occurs in patients receiving **COXITEC**, treatment with **COXITEC** should be stopped.

Caution should be exercised in patients receiving treatment with anticoagulants.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in association with the use of **COXITEC** (see section 4.8). Patients appear to be at higher risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. **COXITEC** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **COXITEC**. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue **COXITEC** and evaluate the patient immediately.

COXITEC may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).
Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and they should only be treated with **COXITEC** after careful consideration.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **COXITEC** therapy In view of **COXITEC's** inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

COXITEC inhibits the synthesis of renal prostaglandins which play a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of **COXITEC** may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of therapy.

Patients at greatest risk of such a reaction are elderly individuals, dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those receiving concomitant treatment with a diuretic, ACE inhibitor or angiotensin-II receptor antagonist or those having undergone major surgical procedures which led to hypovolaemia. In such patients the volume of diuresis and the renal function should be carefully monitored at the beginning of therapy.

COXITEC may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome.

The dose of **COXITEC** in patients with end-stage renal failure on haemodialysis should not exceed 7,5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min).

In patients with mild to moderate renal insufficiency receiving pemetrexed, **COXITEC** should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

Occasional elevations of serum transaminases or other indicators of liver function have been reported. In most cases these have been small and transient increases above the normal range. If the abnormality is significant or persistent, **COXITEC** should be stopped and follow up tests carried out.

No dose reduction is required in patients with clinically stable liver cirrhosis.

Frail or debilitated patients may tolerate side-effects less well and such patients should be carefully supervised. Caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

Induction of sodium, potassium and water retention and interference with natriuretic effects of diuretics may occur with **COXITEC**. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended.

COXITEC may mask symptoms of an underlying infectious disease.

Regular use of NSAIDs such as **COXITEC** during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased (see section 4.6).

Lithium: **COXITEC** has been reported to increase plasma lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and **COXITEC** is not recommended. If this combination appears necessary, lithium plasma

concentrations should be monitored carefully during the initiation, adjustment and withdrawal of **COXITEC** treatment.

For relevant medicine interactions that require particular attention (see section 4.5).

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase kalaemia (see section 4.5). Regular monitoring of potassium values should be performed in such cases.

Some NSAIDs interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Children under the age of 18 years - Safety and efficacy have not been established.

COXITEC should be used with caution in patients with asthma.

Renal Tubular Acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs at higher than recommended doses. NSAID induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Lactose intolerance:

COXITEC tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **COXITEC** tablets.

4.5 Interaction with other medicines and other forms of interaction

Certain medicines or therapeutic groups may promote hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicines, low-molecular-weight or unfractionated heparins, ciclosporin, tacrolimus and trimethoprim.

The onset of hyperkalaemia may depend on whether there are associated factors. This risk is increased when the above-mentioned medicines are co-administered with **COXITEC**.

Other prostaglandin synthetase inhibitors (PSIs) including NSAIDs and salicylates (Acetylsalicylic acid/Aspirin):

Use of two or more NSAIDs concomitantly may result in an increase in side effects such as gastric ulceration and/or bleeding via the synergistic effect. The concomitant use of **COXITEC** with other NSAIDs is not recommended.

Concomitant administration of acetylsalicylic acid (aspirin) given at doses ≥ 500 mg as single intake or ≥ 3 g as total daily amount is not recommended. Because of its lack of platelet effects, **COXITEC** is not a substitute for aspirin or cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with **COXITEC.**

Oral anticoagulants, systemically administered heparin, thrombolytics:

Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. **COXITEC** may enhance the effects of anticoagulants such as warfarin with an increased risk of bleeding (see section 4.4). The concomitant use of **COXITEC** and anticoagulants or heparin administered in the elderly is not recommended. In remaining cases (e.g. preventive doses) of heparin use, caution is necessary due to an increased bleeding risk. If such co-administration cannot be avoided, close monitoring of their effects on coagulation is required.

Lithium:

May result in an increase in plasma lithium concentrations (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and **COXITEC** is not recommended. Monitor lithium plasma concentrations carefully when therapy with **COXITEC** is initiated or withdrawn.

Methotrexate:

COXITEC can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of **COXITEC** is not recommended (see section 4.4). The risk of an interaction between **COXITEC** and methotrexate should be considered, also in patients on a low dosage of methotrexate, especially in patients with impaired renal function. If combination treatment is necessary, the blood cell count and renal function should be monitored. When **COXITEC** and methotrexate are given within 3 days of each other, the plasma level of methotrexate may increase and cause increased toxicity. Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant **COXITEC** treatment, it should be considered that the haematological toxicity of methotrexate can be increased by treatment with **COXITEC**.

Angiotensin-converting enzyme (ACE) inhibitors and other antihypertensive agents:

May result in a decrease in antihypertensive effects by inhibition of vasodilating prostaglandins. **COXITEC** and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment the co-administration of an ACE inhibitor or angiotensin-II antagonists and medicines that inhibit cyclooxygenase may result in further detoriation of renal function, this

may lead to acute renal failure, which is usually reversible. 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 (see section 4.4.).

Concomitant treatment with probenecid leads to reduced excretion and thereby increased effects of **COXITEC.**

Cholestyramine:
May result in a reduced therapeutic effect of **COXITEC** tablets. Cholestyramine binds meloxicam in the gastrointestinal tract leading to a faster elimination of **COXITEC.**

Ciclosporin:
Increase the risk of nephrotoxicity via renal prostaglandin mediated effects. During combined treatment renal function should be assessed regularly.

Tacrolimus should not be combined with **COXITEC** tablets.

Alcohol:
Simultaneous intake may increase the risk of bleeding

Diuretics:
Treatment with **COXITEC** may result in renal impairment if the patient is dehydrated (see section 4.4). Patients receiving **COXITEC** and diuretics should be adequately hydrated and monitored for renal function prior to initiating treatment.

Intrauterine device:

NSAIDs may decrease the efficacy of intrauterine devices.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding, via inhibition of platelet function.

Deferasirox:

The concomitant administration of meloxicam with deferasirox may increase the risk of gastrointestinal adverse reactions. Caution should be exercised when combining these medicinal products.

Pemetrexed*:*

For the concomitant use of **COXITEC** with pemetrexed in patients with creatinine clearance from 45 to 79 mL/min, the administration of **COXITEC** should be paused for 5 days before, on the day of, and 5 days following pemetrexed administration. If a combination of **COXITEC** with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastrointestinal adverse reactions. In patients with creatinine clearance below 45 mL/min the concomitant administration of **COXITEC** with pemetrexed is not recommended.

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), doses of 15 mg **COXITEC** may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be exercised when administering 15 mg **COXITEC** concurrently with pemetrexed to patients with normal function (creatinine clearance ≥ 80 mL/min).

Medicines known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4:

COXITEC is eliminated almost entirely by hepatic metabolism, of which approximately two thirds are mediated by cytochrome (CYP) P450 enzymes (CYP 2C9 major pathway and CYP 3A4 minor pathway) and one third by other pathways, such as peroxidase oxidation. The potential for a pharmacokinetic interaction should be taken into account when **COXITEC** and medicines known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4 are administered concurrently. Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these medicines and **COXITEC**. Patients concomitantly using **COXITEC** with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

No relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine, digoxin and furosemide.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy has not been established. **COXITEC** tablets is contraindicated during pregnancy (see section 4.3). Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. During the first and second trimester of pregnancy, **COXITEC** should not be given.

The use of **COXITEC** tablets during the third trimester of pregnancy may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).

- renal dysfunction, which may progress to renal failure with oligohydramnios the mother and the neonate, at the end of pregnancy, to:
- prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour (see sections 4.3 and 4.4).

Breastfeeding

While no specific experience exists for **COXITEC** in humans, NSAIDs are known to pass into mother's milk. Administration is therefore contraindicated in women who are breastfeeding.

Fertility

The use of **COXITEC** may impair fertility and is not recommended in women attempting to conceive. **COXITEC** may delay ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of **COXITEC** should be considered.

4.7 Effect on ability to drive and use machines

Patients should not operate machinery or drive a vehicle if they experience drowsiness, blurred vision or any other central nervous system effect.

4.8 Undesirable effects

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal.

Table 1: Tabulated list of adverse reactions

System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Anaemia	*Frequent*
	Leukopenia, thrombocytopenia,	*Less frequent*

	neutropenia, eosinophilia, agranulocytosis	
Immune system disorders	Allergic reactions other than anaphylactic or anaphylactoid reaction, angioedema	*Less frequent*
	Anaphylaxis, anaphylactoid reaction, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)*	*Frequency unknown*
Metabolism and nutrition disorders	Weight increase or decrease	*Less frequent*
	Hypokalaemia**	*Frequency unknown*
Cardiac disorders	Peripheral oedema	*Frequent*
	Palpitations, elevated blood pressure (hypertension), angina pectoris, dysrhythmia, tachycardia	*Less frequent*
	Congestive Cardiac failure, oedema, myocardial infarction, cardiovascular thrombotic events	*Frequency unknown*
Vascular disorders	Hypertension, hypotension, flushing	*Less frequent*
	Aggravated hypertension	*Frequency unknown*
Psychiatric disorders	Nightmares, mood altered	*Less frequent*

	Confusions*, disorientation*, depression	*Frequency unknown*
Nervous system disorders	Headache, dizziness, light headedness	*Frequent*
	drowsiness, insomnia, aseptic meningitis	*Less frequent*
	Cerebrovascular incidents (strokes)	*Frequency unknown*
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain,	*Frequent*
	Gastrointestinal bleeding, or ulceration (generally more serious in the elderly), perforation, induction or exacerbation of colitis, gastritis, eructation, oesophagitis, dry mouth, gastroesophageal reflux, dehydration, taste perversion, pancreatitis	*Less frequent*
	Melaena, haematemesis, ulcerative stomatitis, exacerbation of Crohn's disease,	*Frequency unknown*

Renal and urinary disorders	Nephrotic syndrome, glomerulonephritis, interstitial nephritis and papillary necrosis, renal failure, sodium and water retention, hyperkalaemia, hyponatraemia, renal function test abnormal, micturition disorders, acute urinary retention, haematuria, albuminuria	*Less frequent*
	Renal tubular acidosis**	*Frequency unknown*
Hepatobiliary disorders	Hepatitis, liver function disorder (e.g. raised transaminases or bilirubin), hepatotoxicity, idiosyncratic liver abnormality, jaundice	*Less frequent*
Eye disorders	Visual disturbances (such as blurred vision), conjunctivitis, optic nerve reactions	*Less frequent*
Ear and labyrinth disorders	Hearing loss	*Frequent*
	Vertigo, tinnitus	*Less frequent*
Respiratory, thoracic and mediastinal disorders	Bronchospasm	*Frequent*
	Asthma in individuals allergic to aspirin or other NSAIDs	*Less frequent*

Skin and subcutaneous tissue disorders	Pruritis, rash, flushing	*Frequent*
	Urticaria, stomatitis, photosensitivity*, bullous dermatoses, including erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia	*Less frequent*
Reproductive system and breast disorders	Delayed ovulation	*Less frequent*
	Female infertility*	*Frequency unknown*

*Post marketing events

**Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of higher than recommended doses.

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 Overdosage

Signs and symptoms:

Symptoms following acute **COXITEC** overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which may be reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Exacerbation of asthma may occur in asthmatics. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Management of overdosage:

Treatment is symptomatic and supportive as there is no known antidote. Absorption should be reduced by:

- Activated charcoal if patient presents 1 to 2 hours after overdose
- Cholestyramine

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification**:** A. 3.1 Antirheumatics (anti-inflammatory agents).

ATC code: M01AC06

Mechanism of action

Meloxicam, an oxicam (enolic acid) derivative, is a non-steroidal anti-inflammatory compound (NSAID) with analgesic, antipyretic and anti-inflammatory activities. The action of meloxicam is related to inhibition of the enzyme cyclo-oxygenase (COX), resulting in the decreased

formation of prostaglandins (mediators of inflammation) and thromboxanes. A selective COX-2 inhibitory (anti-inflammatory effect) *in vitro* in relation to Cox -1 has been demonstrated. Inhibition of COX-1 (gastrointestinal, renal and platelet effects) *in vivo* occurs. It is suggested that the extent of inhibition of COX-1 *in vivo* is a function of dose and inter-individual variability of meloxicam concentrations.

5.2 Pharmacokinetic properties

Absorption:

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability after oral administration of 89 % and concomitant administration with food does not affect absorption.

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5 to 6 hours. With multiple dosing, steady state conditions were reached within 3 to 5 days.

Once-daily dosing leads to medicine plasma concentrations with a relatively small peak-trough fluctuation in the range of 0,4 – 1,0 µg/mL for 7,5 mg doses and 0,8 – 2,0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively).

Continuous treatment for longer periods (e.g. six months) did not point to any changes in pharmacokinetics compared to steady state pharmacokinetics after two weeks of oral treatment with 15 mg meloxicam/day.

Distribution:

Meloxicam is 99 % protein bound. Meloxicam penetrates into synovial fluid to give concentrations approximately half of those n plasma.

Volume distribution is low, on average 11 L. Inter-individual variation is in the order of 30 – 40 %. The volume of distribution following administration of multiple of multiple doses of meloxicam (7,5 to 15 mg) is about 16 L.

Biotransformation:

Meloxicam is extensively metabolised in the liver (mainly by oxidation). Four different metabolites were identified in urine, which were all pharmacodynamically inactive.
The major metabolite, 5'-carboxymeloxicam (60 % of dose), is formed by oxidation of an intermediate metabolite 5'- hydroxymethylmeloxicam, which is also excreted to a lesser extent (9 % of dose). *In vitro* studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16 % and 4 % of the administered dose, respectively.

Elimination:

Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5 % of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.
The elimination half-life is 15 - 20 hours.
Total plasma clearance amount on average to 8 mL/min.

Linearity/non-linearity:

Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7,5 mg to 15 mg following oral or intramuscular administration.

Special populations

Patients with hepatic/renal insufficiency:

Mild or moderate hepatic insufficiency and mild renal insufficiency do not have a substantial effect on meloxicam pharmacokinetics.
Subjects with moderate renal impairment had significantly higher total meloxicam clearance.
A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and daily dose of 7,5 mg must not be exceeded (see section 4.2).

Elderly:

Elderly male subjects exhibited similar mean pharmacokinetic parameters compared with those of young male subjects. Elderly female patients showed higher AUC-values, increased by 50 – 100 %, and longer elimination half-lives compared with those of young subjects of both genders.

Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate

Lactose monohydrate (Pharmatose 200M)

Microcrystalline cellulose (Avicel PH 101)

Povidone (Kollidon K 30)

Crospovidone (Kollidon CL)

Colloidal silicon dioxide (Aerosil 200)

Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep well closed.

Store at or below 25 ºC

6.5 Nature and contents of container

COXITEC Tablets are available in white HDPE bottles of 100 tablets.

6.6 Special precautions for disposal

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

South Africa

8. REGISTRATION NUMBER:

COXITEC 7,5 mg: 42/3.1/0321

COXITEC 15 mg: 42/3.1/0322

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of registration: 25 November 2011

10. DATE OF REVISION OF TEXT

31 August 2023