Summary Product Characteristics for Pharmaceutical Product

1. Name of the medicinal product

Equicoxia MR

2. Qualitative and quantitative composition

Each tablet contains Paracetamol 500mg, Chlorzoxazone 250mg and Etoricoxib 90 mg

Excipients with known effect

Contains Sodium Benzoate

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Tablet

A blue colour, oblong shaped, film-coated tablets having break line on one side & other side plain.

4. Clinical particulars

4.1 Therapeutic indications

It is indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs ofinflammation associated with acute gouty arthritis, short-term treatment of moderate pain associated with dental surgery. Also, it relieves pain and stiffness caused by muscle strains and sprains.

4.2 Posology and method of administration

Adults and adolescents 16 years of age or older
One tablet daily, one to two hours after meals or as recommended by the physician

Method of administration:
For oral use.

4.3 Contraindications

Equicoxia MR is contraindicated in the following situations:

- Patients sensitive to etoricoxib, paracetamol, chlorzoxazone or any of the excipients of the product.
- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2)inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.

- Pregnancy and lactation
- Severe hepatic dysfunction (serum albumin < 25 g/L or Child-Pugh score ≥10).
- Estimated renal creatinine clearance < 30 mL/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHgand has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Etoricoxib

Gastrointestinal effects
Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of themresulting in fatal outcomes, have occurred in patients treated with etoricoxib.
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 acetylsalicylic acidconcomitantly or patients with a prior history of gastrointestinal disease, such as ulceration andGI bleeding.
There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly withacetylsalicylic 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

Cardiovascular effects
Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with arisk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should beused. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with etoricoxib after carefulconsideration.
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore,antiplatelet therapies should not be discontinued

Renal effects
Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion,

administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, thereby impairing renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose-related response to etoricoxib. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema for any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1 % of patients in clinical trials treated for up to one year with etoricoxib 30, 60 and 90 mg daily.

Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

Paracetamol.

Contains paracetamol. Do not use with any other paracetamol-containing products. Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.

Caution should be exercised in patients with glutathione-depleted states, as the use of paracetamol may increase the risk of metabolic acidosis.

Use with caution in patients with glutathione depletion due to metabolic deficiencies.

Chlorzoxazone

The drug may cause dizziness or drowsiness. Alcohol may increase the effect. Do not drive, use machinery, or do anything that needs alertness until you can do it safely. Avoid alcoholic beverages.

Older adults may be more sensitive to the side effects of this drug, especially drowsiness, or confusion. These side effects can increase the risk of falling.

4.5 Interaction with other medicinal products and other forms of interaction

Etoricoxib

Pharmacodynamic interactions

Oral anticoagulants: In subjects stabilized on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13 % increase in prothrombin time International Normalized Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g., dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. 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.

Acetylsalicylic Acid: In a study of healthy subjects, at a steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis

(low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to the use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended

Cyclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, coadministration of cyclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when etoricoxib and either of these drugs are used in combination.

Pharmacokinetic interactions

Lithium: NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate: Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. etoricoxib 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13 %.

Oral contraceptives: Etoricoxib given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady-state AUC_{0-24hr} of EE by 37 %. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady-state AUC_{0-24hr} of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thromboembolic events in women at risk).

Hormone Replacement Therapy (HRT): Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN) for 28 days, increased the mean steady-state AUC_{0-24hr} of unconjugated estrone (41 %), equilin (76 %), and 17-β-estradiol (22 %). The effect of the recommended chronic doses of etoricoxib (30, 60, and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24hr}) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-

menopausal hormone therapy for use with etoricoxib because the increase in oestrogen exposure might increase the risk of adverse events associated with HRT.

Digoxin: patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolized by sulfotransferases

Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about the effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil)

Rifampicin: Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65 % decrease in etoricoxib plasma concentrations. This interaction may result in the recurrence of symptoms when etoricoxib is co-administered with rifampicin. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended.

Paracetamol

Drugs that induce hepatic microsomal enzymes, such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, with an increased risk of bleeding. The effect appears to increase as the dose of paracetamol is increased, but can occur with doses as low as 1.5-2 g paracetamol per day for at least 5-7 days. Occasional doses have no significant effect.

Probenicid inhibits the glucuronidation of paracetamol which can affect the clearance of paracetamol. This should be considered when these medicines are administered concomitantly.

Paracetamol may affect the pharmacokinetics of chloramphenicol. This interaction should be considered when these medications are administered concomitantly, especially in malnourished patients.

Enzyme-inducing medicines, such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approximately 60%. Other substances with enzyme-inducing properties, e.g. rifampicin and St John's wort (*Hypericum perforatum*) are also suspected of causing lowered concentrations of paracetamol. In addition, the risk of liver damage during

treatment with the maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing agents.

Chlorzoxazone

Chlorzoxazone,calcium/magnesium/potassium/sodium oxybates. Either increase the effects of the other by pharmacodynamic synergism. Avoid or Use Alternate Drugs. Profound sedation, respiratory depression, coma, and death may result if coadministered. Reserve concomitant prescribing of these drugs in patients for whom other treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor closely for signs of respiratory depression and sedation.

Hydrocodone, chlorzoxazone. Either increase the toxicity of the other by pharmacodynamic synergism. Avoid or Use Alternate Drugs. Profound sedation, respiratory depression, coma, anddeath may result if coadministered. Reserve concomitant prescribing of these drugs in patients for whom other treatment options are inadequate. Limit dosages and durations to the minimumrequired. Monitor closely for signs of respiratory depression and sedation.

Chlorzoxazone will increase the level or effect of lonafarnib by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drugs. If coadministration of lonafarnib (a sensitive CYP3A substrate) with weak CYP3A inhibitors is unavoidable, reduce, or continue lonafarnib at the starting dose. Closely monitor for arrhythmias and events (e.g., syncope, heart palpitations) since lonafarnib effect on QT interval is unknown.

Chlorzoxazone, metoclopramide intranasal. Either increase the effects of the other by Other (see comment). Avoid or Use Alternate Drugs. Comment: Avoid the use of metoclopramide intranasal or interacting drugs, depending on the importance of the drug to the patient.

Chlorzoxazone, sodium oxybate. Either increase the effects of the other by pharmacodynamic synergism. Avoid or Use Alternate Drugs. Profound sedation, respiratory depression, coma, anddeath may result if coadministered. Reserve concomitant prescribing of these drugs in patients for whom other treatment options are inadequate. Limit dosages and durations to the minimumrequired. Monitor closely for signs of respiratory depression and sedation.

Sufentanil SL, chlorzoxazone. Either increase the toxicity of the other by pharmacodynamic synergism. Avoid or Use Alternate Drugs. Coadministration may result in hypotension, profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs in patients for whom other treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor closely for signs of respiratory depression and sedation.

4.6 Pregnancy and lactation

Etoricoxib

Pregnancy

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

Breast-feeding

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib must not breastfeed.

Chlorzoxazone has not been evaluated for safe use during pregnancy; therefore, its effects on the fetus are unknown.

4.7 Effects on the ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery. Further, CNS depressant effects of chlorzoxazone may impair driving or operating machinery or the ability to perform other hazardous activities. Thus, patients are advised not to drive vehicles or operate machinery while taking this medicine.

4.8 Undesirable effects

Etoricoxib

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 30 mg, 60 mg or 90 mg up to the recommended dose for up to 12 weeks; in the MEDAL Programme studies for up to 3½ years; in short term acute pain studies for up to 7 days; or in post-marketing experience:

System Organ Class	**Adverse Reactions**	**Frequency Category***
Infections and infestations	Alveolar osteitis	Common
	Gastroenteritis,upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	Anaemia(primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity‡ §	Uncommon

	Angioedema/anaphylactic /anaphylactoid reactions including shock‡	Rare
Metabolism and nutrition disorders	Oedema/fluid retention	Common
	Appetite increase or decrease, weight gain	Uncommon
Psychiatric disorders	Anxiety, depression, mental acuity decreased, hallucinations‡	Uncommon
	Confusion‡, restlessness‡	Rare
Nervous system disorders	Dizziness, headache	Common
	Dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence	Uncommon
Eye disorders	Blurred vision, conjunctivitis	Uncommon
Ear and labyrinth disorders	Tinnitus, vertigo	Uncommon
Cardiac disorders	Palpitations, arrhythmia‡	Common
	Atrial fibrillation, tachycardia‡, congestive heart failure, non-specific ECG changes, angina pectoris‡, myocardial infarction§	Uncommon
Vascular disorders	Hypertension	Common
	Flushing, cerebrovascular accident§, transient ischaemic attack, hypertensive crisis‡, vasculitis‡	Uncommon
Respiratory, thoracic and mediastinal disorders	Bronchospasm‡	Common
	Cough, dyspnoea, epistaxis	Uncommon
Gastrointestinal disorders	Abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer	Common
	Abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis‡	Uncommon
Hepatobiliary disorders	ALT increased, AST increased	Common
	Hepatitis‡	Rare
	Hepatic failure‡, jaundice‡	Rare†
Skin and subcutaneous tissue disorders	Ecchymosis	Common
	Facial oedema, pruritus, rash, erythema‡, urticaria‡	Uncommon
	Stevens-Johnson syndrome‡, toxic epidermal necrolysis‡, fixed drug eruption‡	Rare†
Musculoskeletal and connective tissue disorders	Muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	Proteinuria, serum creatinine increased, renal failure/renal insufficiency‡(see section 4.4)	Uncommon
General disorders and administration site conditions	Asthenia/fatigue, flu-like disease	Common

	Chest pain	Uncommon
Investigations	Blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased	Uncommon
	Blood sodium decreased	Rare

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000).

‡ This adverse reaction was identified through post-marketing surveillance. Its reported frequency has been estimated based upon the highest frequency observed across clinical trial data pooled by indication and approved dose.

†The frequency category of "Rare" was defined per the Summary of Product Characteristics (SmPC) guidance (rev. 2, Sept 2009) on the basis of an estimated upper bound of the 95 % confidence interval for 0 events given the number of subjects treated with ARCOXIA in the analysis of the Phase III data pooled by dose and indication (n = 15,470).

ß Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy".

§Based on analyses of long-term placebo and active controlled clinical trials, selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1 % per year based on existing data (uncommon).

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome.

Paracetamol

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including thrombocytopenic purpura, methemoglobinemia and agranulocytosis, but these were not necessarily related to paracetamol.

Chlorzoxazone

Chlorzoxazone is usually well tolerated. It is possible in rare instances that chlorzoxazone may have been associated with gastrointestinal bleeding. Drowsiness, dizziness, lightheadedness, malaise, or overstimulation may be noted by an occasional patient. Rarely, allergic-type skin rashes, petechiae, or ecchymoses may develop during treatment. Angioneurotic edema or anaphylactic reactions are extremely rare. Rarely, a patient may note discolouration of the urine resulting from a phenolic metabolite of chlorzoxazone. However, this finding is of no known clinical significance.

Reporting of suspected adverse reactions:

Healthcare professionals are asked to report any suspected adverse reactions via the pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Etoricoxib

In clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

Paracetamol

Symptoms: Ingestion of 5gm or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Immediate treatment is essential in the management of paracetamol overdose. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine (approved antidote) may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion.

Chlorzoxazone

Symptoms: Initial symptoms following chlorzoxazone overdose include gastrointestinal disturbances such as nausea, vomiting, or diarrhoea together with drowsiness, dizziness, lightheadedness or headache. Early in the course, there may be malaise or sluggishness followed by marked loss of muscle tone, making voluntary movement impossible. The deep tendon reflexes may be decreased or absent. The sensorium remains intact, and there is no peripheral loss of sensation. Respiratory depression may occur with rapid, irregular

respiration and intercostal and substernal retraction. There may be a decrease in blood pressure as well.

Gastric lavage or induction of emesis should be carried out, followed by administration of activated charcoal. Thereafter, treatment is entirely supportive. If respirations are depressed, oxygen and artificial respiration should be employed and a patent airway assured by the use of an oropharyngeal airway or endotracheal tube. Hypotension may be counteracted by the use of dextran, plasma, concentrated albumin or a vasopressor agent such as norepinephrine. Cholinergic drugs or analeptic drugs are of no value and should not be used

5. Pharmacological properties

5.1 Pharmacodynamic properties

Etoricoxib

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs.

Mechanism of Action

Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. Across clinical pharmacology studies, ARCOXIA produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

Paracetamol

Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of aspirin but with no demonstrable anti-inflammatory activity. Paracetamol is less irritant to the stomach than aspirin. It does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

Analgesic Action: The central analgesic action of paracetamol resembles that of aspirin. It produces analgesia by raising the pain threshold.

Antipyretic Effect: The antipyretic effect of paracetamol is attributed to its ability to inhibit COX in the brain where the peroxide tone is low. Recent evidence suggests inhibition of COX-3 (believed to be a splice variant product

of the COX-1 gene) and could represent a primary central mechanism by which paracetamol decreases pain and, possibly, fever.

Chlorzoxazone

Chlorzoxazone is a centrally-acting skeletal muscle relaxant with sedative properties; it is used for the symptomatic treatment of painful muscle spasm Chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasms of varied etiology. The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles. Pain relief is postulated to be due to alterations in the perception of pain. Chlorzoxazone is not associated with significant anticholinergic effects.

5.2 Pharmacokinetic properties

Etoricoxib

Absorption

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100 %. Following 120 mg once-daily dosing to a steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 µg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{0-24hr}) was 37.8 µg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36 % decrease in C_{max} and an increase in T_{max} by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution

Etoricoxib is approximately 92 % bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/mL. The volume of distribution at steady state (V_{dss}) was approximately 120 L in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Biotransformation

Etoricoxib is extensively metabolised with < 1 % of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the

6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination

Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70 % of radioactivity was recovered in urine and 20 % in faeces, mostly as metabolites. Less than 2 % was recovered as an unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady-state concentrations of etoricoxib are reached within seven days of once-daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 mL/min.

Paracetamol

Absorption
Paracetamol is well absorbed by the oral route. The plasma half-life is about 2 hours.

Distribution
Plasma protein binding is negligible at the usual therapeutic concentration but increases with increasing concentrations. Acetaminophen is, relatively, uniformly distributed throughout most body fluids. The plasma half-life is ($t_{½}$) 2-3 hours and the effect after an oral dose lasts for 3-5 hours.

Metabolism
Paracetamol is primarily metabolized in the liver by conjugation with glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is metabolized by oxidation and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates.

Elimination
Excretion occurs via the kidneys. Of a therapeutic dose, 2-3% is excreted unchanged, 80-90% as glucuronide and sulphate, and a smaller amount as cystein and mercapturic acid derivatives.

Chlorzoxazone
Absorption of chlorzoxazone from the gastrointestinal tract is rapid and complete. Blood levels of chlorzoxazone can be detected in humans during the first 30 minutes and peak levels occur approximately 1 to 2 hours after oral administration. Chlorzoxazone is well distributed, with the highest concentrations found in plasma and fat, and lower concentrations found in the liver, muscle, brain and kidneys. The volume of distribution is roughly 14 L. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6- hydroxychlorzoxazone, and excreted in the urine

primarily as the glucuronide metabolite. Less than 1% of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours; 74% of the metabolite is excreted within 10 hours. The elimination half-life of chlorzoxazone is about 1 hour

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose
Starch (Maize starch)
Povidone K-30
Sodium Benzoate
Purified water
Magnesium stearate
Purified Talc
Sodium starch glycolate
ColloidalAnhydrous Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of the container

Alu-PVC blister pack
Pack size: 1x10 tablets

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder and manufacturing site addresses

Equival Enterprises Ltd.
P.O. Box 103701 – 00101 NAIROBI.
Telephone No: + 254 751 006 373
Email: equivalenterprisesltd@gmail.com

Manufacturing site address:

Centurion Laboratories Pvt Ltd
Plot No. P-2, Savali Bio-Tech Park, At-Manjusar,
Tal: Savali Dist- Vadodara-391775, India.

8. Marketing authorisation number(s)

CTD10181- Equicoxia MR

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 22-May-2023

10. Date of revision of the text

15-Sep-2023

11. Dosimetry:

Not Applicable

12. Instructions for preparation of radiopharmaceuticals:

Not Applicable