Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

PARACE-MR

2. Qualitative and quantitative composition

Each film coated tablet contains:
Aceclofenac 100mg
Paracetamol 500mg
Chlorzoxazone 375mg
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet

White coloured capsule shaped film coated tablet with breakline on one side and plain on the other.

4. Clinical particulars

4.1 Therapeutic indications

Parace-MR is indicated for relief of acute to moderate pain and inflammation in Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, lower back pain, dental pain, gynaecological pain and pain relief in inflammatory conditions associated with the ear, nose & throat. It is also used in the symptomatic management of painful muscle spasm associated with musculoskeletal conditions.

4.2 Posology and method of administration

For oral administration.
Adults: Usual dose is 1 tablet to be administered twice daily. PARACE-MR Tablets should be preferably administered with or after food. The tablet should be swallowed whole with water. • The maximum recommended dose of aceclofenac is 200 mg daily in divided doses.
• The maximum recommended dose of paracetamol is 4 g daily in divided doses.
• Maximum dosage of chlorzoxazone is 3,000 mg per day in divided doses.

4.3 Contraindications

PARACE-MR Tablets are contraindicated in the following:

• Known hypersensitivity to aceclofenac or to paracetamol or to chlorzoxazone or to any component of the formulation.

• Active or history of recurrent peptic ulcer, bleeding or bleeding disorders.

• History of gastrointestinal (GI) bleeding or perforation, relating to previous NSAID therapy.

- Severe heart failure, hepatic failure and renal failure.

- Patients with established congestive heart failure (NYHA class II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease

- During the last trimester of pregnancy.

- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.

- Known intolerance to chlorzoxazone.

4.4 Special warnings and precautions for use

Aceclofenac

Gastrointestinal (GI) Bleeding, Ulceration and Perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID dose, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase GI risk. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin. When GI bleeding or ulceration occurs in patients receiving aceclofenac, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated. Hypersensitivity Reactions: As with other NSAIDs, allergic reactions (including anaphylactic reactions), can occur without earlier exposure to the drug.

Dermatological: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Respiratory: Use with caution in patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Hematological: Aceclofenac may reversibly inhibit platelet aggregation. Patients with defect of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), aceclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Use of aceclofenac in patients with hepatic porphyria may trigger an attack.
Renal: Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of aceclofenac.

Cardiovascular: Caution is required in patients with a history of hypertension and/or heart failure, as fluid retention and edema have been reported in association with NSAID therapy. Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and edema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac. Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aceclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Fertility: The use of aceclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of aceclofenac should be considered.

Other NSAIDs (Including COX-2 Selective Inhibitors): The use of aceclofenac with concomitant aspirin/NSAIDs including

cyclooxygenase-2 (COX-2) selective inhibitors should be avoided as this may increase the risk of adverse effects including the risk of GI bleeding.

Long Term Treatment: Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. As a precautionary measure, all patients who are receiving NSAIDs for longer time should be regularly monitored for renal failure, hepatic function and blood counts.

Paracetamol

Hepatotoxicity: Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Other Paracetamol-Containing Products: Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.

Renal and Hepatic Impairment: Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.
Alcohol: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use, although rarely.

Chlorzoxazone

Hepatotoxicity: Serious (including fatal) hepatocellular toxicity has been reported rarely in patients receiving chlorzoxazone. The mechanism is unknown but appears to be idiosyncratic and unpredictable. Factors predisposing patients to this rare event are not known. Patients should be instructed to report early signs and/or symptoms of hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. Chlorzoxazone should be discontinued immediately if any of these signs or symptoms develops. Chlorzoxazone use should also be discontinued if a patient develops abnormal liver enzymes (e.g., AST, ALT, alkaline phosphatase and bilirubin).

Alcohol/ CNS Depressants: The concomitant use of alcohol or other CNS depressant drugs may have an additive effect.

Allergy: Chlorzoxazone should be used with caution in patients with known allergies or with a history of allergic reactions to drugs. If a sensitivity reaction occurs such as urticaria, redness, or itching of the skin, the drug should be stopped.

4.5 Interaction with other medicinal products and other forms of interaction

Aceclofenac

Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentration of lithium and thus, increases their risk of its toxicity.

Cardiac Glycosides (Digoxin): Through their renal effects, NSAIDs may increase plasma glycoside levels, exacerbate cardiac failure and reduce the glomerular filtration rate (GFR) in patients receiving glycosides.

Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: Like other NSAIDs, aceclofenac may enhance the activity of anticoagulants such as warfarin. Close monitoring of patients on combined anticoagulant and aceclofenac therapy should be undertaken.

Antihypertensive Drugs: NSAIDs may reduce the effect of antihypertensives. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g., dehydrated patients or elderly patients) when angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. 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.

Antidiabetic Agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycemic and hyperglycemic effects. Thus, with aceclofenac, consideration should be given to adjustment of the dosage of hypoglycemic agents.

Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

Mifepristone: NSAIDs should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Concomitant administration of aceclofenac with corticosteroids may increase the risk of GI ulceration or bleeding.

Anti-Platelet Agents and Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of aceclofenac with these drugs may increase the risk of GI bleeding.

Ciclosporin: Ciclosporin nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

Quinolone Antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving a NSAID

Paracetamol

Cholestyramine: The rate of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Concurrent administration of paracetamol and chloramphenicol may markedly retard the elimination of chloramphenicol and thus, increases plasma concentration of chloramphenicol which leads to risk of its harmful effects. Monitoring of chloramphenicol plasma levels is recommended while combining paracetamol with chloramphenicol injection.

Alcohol, Anticonvulsants, and Isoniazid: Concomitant administration of alcohol, anticonvulsants, and isoniazid with paracetamol may increase risk of hepatotoxicity.

Chlorzoxazone

CNS Depressants: Patients receiving antipsychotics, antianxiety agents or other CNS depressants concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Alcohol: Concomitant use of alcohol with chlorzoxazone will exacerbate the CNS depression and should be avoided. Patients suffering from alcoholism or currently under ethanol intoxication should not use chlorzoxazone.

Codeine/Dihydrocodeine/Hydrocodone: Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with skeletal muscle relaxants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect.

4.6 Fertility, pregnancy, and lactation

Pregnant Women

Pregnancy Category: Aceclofenac - C; Paracetamol - B; Chlorzoxazone - C. There is no information on the use of aceclofenac during pregnancy. Use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. It may also delay onset of labour and increase its duration. NSAID use may also result in premature closure of the foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the new born, delay onset and increase duration of labour. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage. Chlorzoxazone has not been evaluated for safe use during pregnancy; therefore, its effects on the fetus are unknown. Based on its aceclofenac content, PARACE-MR Tablets should not be used during the first two trimesters of pregnancy or labor unless the potential benefit to the patient outweighs the possible risk to fetus; further, its use in the last trimester of pregnancy is contraindicated. There are no studies on the effects of aceclofenac and chlorzoxazone during labor or delivery. In animal studies, NSAIDs inhibit prostaglandin synthesis, causes delayed parturition, and increase the incidence of stillbirth. Thus, PARACE-MR Tablets has not been recommended for use in labor or delivery pain.

Lactating Women Paracetamol is excreted in breast milk, but not in significant amounts. There is no information on the secretion of aceclofenac in human milk. It is not known if chlorzoxazone is distributed into breast milk; however, the molecular weight of the drug is low enough that excretion into breast milk is likely. However, the effect of chlorzoxazone on a nursing infant is unknown. Due to lack of safety data, PARACE-MR Tablets are not recommended for use in lactating women.

Paediatric

Patients Safety and effectiveness of this combination product has not been established in paediatric patients. Thus, PARACE-MR Tablets are not recommended for use in children.

Geriatric Patients

Elderly patients with normal renal and hepatic function and without gastrointestinal (GI) disorders may be given the same dose as recommended for adults. The elderly have an increased frequency of adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs), especially GI bleeding and perforation which may be fatal. Thus, caution should be exercised while administration of NSAIDs, including aceclofenac, to older patients. Paracetamol is mainly excreted by the kidney, and the risk of adverse reactions to paracetamol may be greater in patients with impaired renal function. Chlorzoxazone may be used with extreme caution in geriatric patients due to ability of chlorzoxazone to cause central nervous system (CNS) depression, potentially irreversible hepatotoxicity, or other side effects. Generally, skeletal

muscle relaxants including chlorzoxazone are poorly tolerated by older adults. If needed, PARACE-MR Tablets should be used with extreme caution in this population.

Renal Impairment Patients

PARACE-MR Tablets are contraindicated in patients with severe renal impairment or in patients with preexisting renal disease. Generally, no dosage adjustments are needed but, caution is advised and it may be useful to monitor renal function periodically in patients with mild to moderate renal impairment.

Hepatic Impairment Patients

PARACE-MR Tablets should be used cautiously, if at all, in patients with a previous history of liver disease. PARACE-MR Tablets should not be used in patients with active hepatic disease or hepatitis; further, its use is contraindicated in patients with severe hepatic impairment.

4.7 Effects on ability to drive and use machines.

Undesirable effects such as dizziness, drowsiness, fatigue, and visual disturbances are possible after taking NSAIDs, including aceclofenac. 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

Aceclofenac

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are GI disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional dizziness. If serious adverse reactions occur, aceclofenac should be withdrawn. Gastrointestinal: The most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely. Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of a non-specific allergic reaction and/or anaphylaxis or respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea. Cardiovascular and Cerebrovascular: Edema, hypertension, palpitation, flushing, hot flushes, vasculitis and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). Neurological and Special Senses: Optic neuritis, somnolence,

reports of aseptic meningitis (especially in patients with existing auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, malaise, confusion, and drowsiness. Renal: Interstitial nephritis. Hematological: Agranulocytosis, aplastic anaemia. Miscellaneous: In patients with varicella, serious cutaneous and soft tissue infections have been reported in association with NSAID treatment. Other rarely reported adverse reactions of aceclofenac include the following: Renal and Urinary: Renal insufficiency, abnormal serum creatinine levels, increased blood urea, renal failure, nephrotic syndrome. Respiratory: Dyspnea, bronchospasm, stridor. Hepatic: Abnormal hepatic enzyme levels, hepatitis, jaundice, increased blood alkaline phosphatase. Blood and Lymphatic System: Anemia, bone marrow depression, granulocytopenia, thrombocytopenia, neutropenia, hemolytic anemia. Skin and Subcutaneous Tissue Disorders: Pruritus, rash, photosensitivity reactions, dermatitis urticaria, angioedema, purpura, erythema multiforme, exfoliative dermatitis, bullous dermatoses, severe mucocutaneous skin reactions (including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) Ear and Labyrinth Disorders: Tinnitus, vertigo. Eye Disorders: Visual disturbance. Nervous System: Paraesthesia, tremor, somnolence, headache, dysgeusia. Psychiatric Disorders: Depression, abnormal dreams, confusion, hallucinations, insomnia. Metabolism: Hyperkalemia. General Disorders: Edema, fatigue, leg cramps.

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, methemoglobenemia 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 discoloration 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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Aceclofenac

Symptoms: There are no human data available on the consequences of aceclofenac overdose. Symptoms of overdose include headache, nausea, vomiting, epigastric pain, GI irritation, GI bleeding. Rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, and occasionally convulsions may occur. In cases of significant poisoning acute renal failure and liver damage are possible.

Treatment: If overdose with aceclofenac occurs, absorption should be prevented as soon as possible by means of gastric lavage and treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, GI irritation, and respiratory depression. Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Renal and liver function should be closely monitored.

Paracetamol

Symptoms: Ingestion of 5 gram 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, hemorrhage, 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.

Treatment: 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 diarrhea together with drowsiness, dizziness, lightheadedness or headache may occur. 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.

Treatment: 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 use of an oropharyngeal airway or endotracheal tube. Hypotension may be counteracted by 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

Aceclofenac ATC code: M01A B16

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with marked analgesic and antiinflammatory properties

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (COX). COX enzymes are involved in conversion of arachidonic acid into prostaglandin (PGs). Prostaglandins are usually responsible for causing pain, inflammation, and fever. Aceclofenac blocks the enzyme COX and thereby inhibit PGs synthesis, thus, produces analgesic and anti-inflammatory effects.

Paracetamol ATC Code: N02 BE01

Paracetamol is a centrally acting analgesic and antipyretic agent.

Analgesic Effect: The mechanism of analgesic action of paracetamol has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking painimpulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic Effect: Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

Chlorzoxazone ATC Code: M03BB03

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 spasm 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

Aceclofenac

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 liters. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug. The main metabolite detected in plasma is 4'- hydroxyaceclofenac. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

Paracetamol

Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

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

No data available.

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch
Microcrystalline Cellulose
Gelatin
Methyl paraben
Propyl paraben
Talcum
Magnesium stearate
Sodium Starch Glycolate
Aerosil
Acdisol
Ready mix colour ICS 7049 (Tartrazine)
Methylene Dichloride
Isopropyl Alcohol

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage:

Store in a dry place below 30˚C. Protect from light.

6.5 Nature and contents of container

Packed in printed Aluminium/PVC foil in unit box alongside with insert

Pack size 3 x 10'S Blister pack

6.6 Special precautions for disposal and other handling:

No special requirements

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Symbiotica Bioceutical Ltd
Manufacturing site address:
Vapi Care Pharma Pvt. Ltd.
Plot No. : 225/3, G.I.D.C., Near Morarji Circle, India

8. Marketing authorization number

CTD9925

9. Date of first registration

03/07/2023

10. Date of revision of the text:

17/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable