SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product

COXCEE MR (CELECOXIB, PARACETAMOL & CHLORZOXAZONE TABLETS)

2. Qualitative and Quantitative Composition

Each Film coated tablet contains:
Celecoxib BP.....200 mg.
Paracetamol BP.....325 mg.
Chlorzoxazone.....250 mg.

3. Pharmaceutical Form

Film Coated Tablets

Yellow coloured, oblong shaped, biconvex, film coated tablet having break-line on one side & plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COXCEE MR Tablet is a combination medicine which may be used for the treatment of pain, swelling, and other symptoms associated with muscle spasms. It may also be used to treatment symptoms such as pain, swelling, etc. associated with musculoskeletal and joint disorders. Patients are advised to undergo appropriate physical therapy and rest, as necessary, along with this medicine to obtain the best possible effect.
It Can also be used to treat acute pain from various sources, juvenile rheumatoid arthritis in children over 2, ankylosing spondylitis, and primary dysmenorrhea.
Acute inflammation and pain associated with muscle spasm
Musculoskeletal Pain and inflammation
This medicine may be used to relieve symptoms such as pain, swelling, redness, etc. associated with arthritis, sports injuries, strains and sprains, spondylitis, etc

4.2 Posology and method of administration

Posology
As the cardiovascular (CV) risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Osteoarthritis
The usual recommended daily dose is 200 mg taken once daily or in two divided doses. In some patients, with insufficient relief from symptoms, an increased dose of 200 mg twice daily may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.
Rheumatoid arthritis
The initial recommended daily dose is 200 mg taken in two divided doses. The dose may, if needed, later be increased to 200 mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.
Ankylosing spondylitis
The recommended daily dose is 200 mg taken once daily or in two divided doses. In a few patients, with insufficient relief from symptoms, an increased dose of 400 mg once daily or in two divided doses may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.
The maximum recommended daily dose is 400 mg for all indications.
Special populations
Elderly
As in younger adults, 200 mg per day should be used initially. The dose may, if needed, later be increased to 200 mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50 kg.
Hepatic impairment
Treatment should be initiated at half the recommended dose in patients with established moderate liver impairment with a serum albumin of 25-35 g/l. Experience in such patients is limited to cirrhotic patients.
Renal impairment
Experience with celecoxib in patients with mild or moderate renal impairment is limited, therefore such patients should be treated with caution.
CYP2C9 poor metabolizers
Patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose.
Paediatric population
Celecoxib is not indicated for use in children.

Method of administration
Tablets for oral use.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Known hypersensitivity to sulphonamides.
Active peptic ulceration or gastrointestinal (GI) bleeding.

Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid(aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 (cyclooxygenase-2) inhibitors.
In pregnancy and in women of childbearing potential unless using an effective method of contraception. Celecoxib has been shown to cause malformations in the two animal species studied. The potential for human risk in pregnancy is unknown, but cannot be excluded.
Breast feeding (see sections 4.6 and 5.3).
Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score >10).
Patients with estimated creatinine clearance <30 ml/min.
Inflammatory bowel disease.
Congestive heart failure (NYHA II-IV).
Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Gastrointestinal (GI) effects
Upper and lower gastrointestinal complications (perforations, ulcers or bleedings [PUBs]), some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or antiplatelet drugs (such as acetylsalicylic acid) or glucocorticoids concomitantly, patients using alcohol or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.
There is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).
A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1).
Concomitant NSAID use
The concomitant use of celecoxib and a non- aspirin NSAID should be avoided.
Cardiovascular effects
Increased number of serious cardiovascular events, mainly myocardial infarction, has been found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib at doses of 200 mg BID and 400mg BID compared to placebo (see section 5.1).
As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. The patient's need for symptomatic relief and response to

therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1).
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with celecoxib after careful consideration (see section 5.1).
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).
Fluid retention and oedema
As with other medicinal products known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.
Hypertension
As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.
Hepatic and renal effects
Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.
NSAIDs, including celecoxib, may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, angiotensin converting enzyme (ACE)-inhibitors, angiotensin II receptor antagonists and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with celecoxib.
Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis and, hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment (see section 4.8).
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of celecoxib therapy should be considered.
CYP2D6 inhibition
Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated medicinal products that are metabolised by CYP2D6 (see section 4.5).

CYP2C9 poor metabolisers
Patients known to be CYP2C9 poor metabolisers should be treated with caution (see section 5.2).
Skin and systemic hypersensitivity reactions
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 celecoxib (see section 4.8). Patients appear to be at highest risk for 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. Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome) have been reported in patients receiving celecoxib (see section 4.8). Patients with a history of sulfonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
General
Celecoxib may mask fever and other signs of inflammation.
Use with oral anticoagulants
In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported. Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with celecoxib is initiated or celecoxib dose is changed (see section 4.5). Concomitant use of anticoagulants with NSAIDS may increase the risk of bleeding. Caution should be exercised when combining celecoxib with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).
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 hepatoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. Tablet should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. Tablet use should also be discontinued if a patient develops abnormal liver enzymes (e.g., AST, ALT, alkaline phosphatase and bilirubin).
The concomitant use of alcohol or other central nervous system depressants may have an additive effect.
If sensitivity reaction occurs such as urticaria, redness, or itching of the skin, the drug should be stopped. If any symptoms suggestive of liver dysfunction are observed, the drug should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Celecoxib
Celecoxib is an inhibitor of CYP2D6. During celecoxib treatment, the plasma concentrations of the CYP2D6 substrate dextromethorphan were increased by 136%. The plasma concentrations of drugs that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of drugs which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic drugs, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.
In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this *in vitro* finding is unknown. Examples of drugs which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.
In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethistherone /35 microg ethinylestradiol).
Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.
In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.
In healthy subjects, co-administration of celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in C_{max} of 16% and in AUC of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

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 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.

Chlorzoxazone
Interaction with Medicine
Amitriptyline

Tramadol
Codeine
Methadone
Pentazocine
Alprazolam
Disease interactions
Liver Disease
This medicine is not recommended for use in patients with a known history of liver diseases due to the increased risk of serious adverse effects and worsening of the patient's condition. Replacement with a suitable alternative should be done under your doctor's supervision.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see sections 4.3 and 5.3). Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductusarteriosus during the last trimester.
During the second or third trimester of pregnancy, NSAIDs including celecoxib may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible.
Celecoxib is contraindicated in pregnancy and in women who can become pregnant (see section 4.3 and 4.4). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Breast-feeding
Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. Women who take celecoxib should not breastfeed.

Fertility
Based on the mechanism of action, the use of NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.
Use of Chlorzoxazone has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgement of the physician, the potential benefits outweigh the possible risks.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.CNS depressant effects of chlorzoxazone may impair driving or operating machinery or the ability to perform other hazardous activities.

4.8 Undesirable effects

Celecoxib

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: 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), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.

Adverse reactions and their frequencies reported in Table 1 are based on the main registration studies.

Table 1. Adverse Drug Reactions in Celecoxib Clinical Trials and Surveillance Experience (MedDRA Preferred Terms)[1,2,3]

Infections and infestations	
Common:	Sinusitis, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	
Uncommon:	Anemia
Rare:	Leucopenia, thrombocytopenia
Not known:	Pancytopenia
Immune system disorders	
Common:	Allergy aggravated
Not known:	Serious allergic reactions, anaphylactic shock, anaphylaxis
Metabolism and nutrition disorders	
Uncommon:	Hyperkaelemia
Psychiatric disorders	
Common:	Insomnia
Uncommon:	Anxiety, depression, tiredness
Rare:	Confusion
Not known:	Hallucinations
Nervous system disorders	
Common:	Dizziness, hypertonia
Uncommon:	Paraesthesia, somnolence, cerebral infarction[1]

Rare:	Ataxia, taste alteration
Not known:	Headache, aggravated epilepsy, meningitis aseptic, ageusia, anosmia, fatal intracranial haemorrhage
Eye disorders	
Uncommon:	Blurred vision
Not known:	Conjunctivitis, ocular haemorrhage, retinal artery or vein occlusion
Ear and labyrinth disorders	
Uncommon:	Tinnitus, hypoacusis
Cardiac disorders	
Common:	Myocardial infarction
Uncommon:	Heart failure, palpitations, tachycardia
Not known:	Arrhythmia
Vascular disorders	
Very common:	Hyper-tension
Uncommon:	Hypertension aggravated
Not known:	Flushing, vasculitis, pulmonary embolism
Respiratory, thoracic, and mediastinal disorders	
Common:	Pharyngitis, rhinitis, cough, dyspnoea
Not known:	Bronchospasm
Gastrointestinal disorders	
Common:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia
Uncommon:	Constipation, eructation, gastritis, stomatitis, aggravation of gastrointestinal inflammation
Rare:	Duodenal, gastric, oesophageal, intestinal, and colonic ulceration; intestinal perforation; oesophagitis, melaena; pancreatitis
Not known:	Nausea, gastrointestinal haemorrhage, colitis/colitis aggravated
Hepatobiliary disorders	
Uncommon:	Abnormal hepatic function, increased SGOT and SGPT
Rare:	Elevation of hepatic enzymes
Not known:	Hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), liver necrosis, hepatitis jaundice
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus

Uncommon:	Urticaria, mouth pain and sores
Rare:	Alopecia, photosensitivity
Not known:	Ecchymosis, bullous eruption, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) or hypersensitivity syndrome, angioedema, acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
Uncommon:	Leg cramps
Not known:	Arthralgia, myositis
Renal and urinary disorders	
Uncommon:	Increased creatinine, BUN increased
Not known:	Acute renal failure, interstitial nephritis, hyponatraemia
Reproductive system and breast disorders	
Not known:	Menstrual disorder NOS
General disorders and administrative site conditions	
Common:	Flu-like symptoms, peripheral oedema/ fluid retention
Not known:	Chest pain

Some common adverse effects include gastro-intestinal disorders (dyspepsia, abdominal pain, nausea), rash, ruber, urticaria, symptoms of enuresis, headache, dizziness, and drowsiness.

Paracetamol:
Paracetamol is metabolized primarily in the liver, where most of it is converted to inactive compounds. Adverse effects of paracetamol are rare. Very rare cases of serious skin reactions have been reported. There have been reports of blood dyscrasias including thrombocytopenia purpura, methaemoglobenaemia and agranulocytosis, but these were not necessarily causality related to paracetamol.

Chlorzoxazone:
Occasional patients may develop gastrointestinal disturbances. 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. There is no evidence that the drug will cause renal damage. Rarely, a patient may note discoloration of the urine resulting from a phenolic metabolite of chlorzoxazone. This finding is of no known clinical significance.

Reporting of adverse Effects

Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Celecoxib
There is no clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects for nine days without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment. Dialysis is unlikely to be an efficient method of drug removal due to high protein binding.
Symptoms: Initially, gastrointestinal disturbances such as nausea, vomiting, or diarrhea together with drowsiness, dizziness, light headedness 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 intercostals and substernal retraction. The blood pressure is lowered, but shock has not been observed.
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.

Paracetamol
Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors.

Chlorzoxazone
Symptoms: Initially, gastrointestinal disturbances such as nausea, vomiting, or diarrhea together with drowsiness, dizziness, light-headedness 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 substernal retraction. The blood pressure is lowered, but shock has not been observed.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Celecoxib – Celecoxib is a member of class of pyrazoles that is 1H-pyrazole which is substituted at positions 1, 3 & 5 by 4-sulfamoylphenyl, trifluoromethyl & p-tolyl groups, respectively. A cyclooxygenase-2 inhibitor, it is used in the treatment of arthritis.

Paracetamol – Paracetamol is a medication used to treat pain and fever. It is typically used for mild to moderate pain relief. There is mixed evidence for its use to relieve fever in children. It is often sold in combination with other medications, such as in many cold medications. Paracetamol is also used for severe pain, such as cancer pain and pain after surgery, in combination with opioid pain medication. It is typically used either by mouth or rectally but is also available by injection into a vein. Effects last between 2 to 4 hours.

Chlorzoxazone – Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain or discomfort. It acts on the spinal cord by depressing reflexes. Possible side effects include dizziness, lightheadedness, malaise, nausea, vomiting, and liver dysfunction. Used with acetaminophen it has added risk of hepatoxicity, which is why the combination is not recommended. It can also be administered for acute pain in general and for tension headache (muscle contraction headache).

MECHANISM OF ACTION:

Celecoxib

Celecoxib is a non-steroidal agent with marked anti-inflammatory and analgesic properties.

Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. COX-2 is expressed heavily in inflamed tissues where it is induced by inflammatory mediators. The inhibition of this enzyme reduces the synthesis of metabolites that include prostaglandin E2 (PGE2), prostacyclin (PGI2), thromboxane (TXA2), prostaglandin D2 (PGD2), and prostaglandin F2 (PGF2). Resultant inhibition of these mediators leads to the alleviation of pain and inflammation.

By inhibiting prostaglandin synthesis, non-steroidal anti-inflammatory drugs (NSAIDs) cause mucosal damage, ulceration and ulcer complication throughout the gastrointestinal tract. Celecoxib poses less of an ulceration risk than other NSAIDS, owing to its decreased effect on gastric mucosal prostaglandin synthesis when compared to placebo.

Celecoxib exerts anticancer effects by binding to the cadherin-11 (CDH11) protein, which is thought to be involved in the progression of tumors, and inhibiting the 3-phosphoinositide-dependent kinase-1 (PDK-1) signaling mechanism. In addition, celecoxib has been found to inhibit carbonic anhydrase enzymes 2 and 3, further enhancing its anticancer effects.
As mentioned in the pharmacodynamics section of this drug entry, celecoxib may cause an increased risk of thrombotic events. The risk of thrombosis resulting from COX-2 inhibition is caused by the vasoconstricting actions of thromboxane A2, leading to enhanced platelet aggregation, which is uncontrolled when the actions of prostacyclin, a platelet aggregation inhibitor, are suppressed through the inhibition of COX-2.

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
A centrally acting central muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain.

5.2 Pharmacokinetic properties

Celecoxib
Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour.
Celecoxib is mainly eliminated by metabolism. Less than 1% of the dose is excreted unchanged in urine. Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes
Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment.
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in

human plasma i.e., a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.
The plasma concentration of celecoxib is approximately 100% increased in elderly women (>65 years). Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

Paracetamol
Paracetamol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine, mainly as glucuronide and sulphate conjugates.

Chlorzoxazone
Blood levels of Chlorzoxazone can be detected in people during the first 30 minutes and peak levels may be reached, in the majority of the subjects, in about 1 to 2 hours after oral administration of Chlorzoxazone. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than one percent of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

5.3 Preclinical safety data:
Non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity beyond those addressed in section 4.4, 4.6, and 5.1 of the SmPC.
Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC0-24), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC0-24 at 200 mg twice daily) throughout organogenesis. These effects are expected following inhibition of prostaglandin synthesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival.
Celecoxib was excreted in rat milk. In a peri-post natal study in rats, pup toxicity was observed.
In a two-year toxicity study an increase in nonadrenal thrombosis was observed in male rat at high doses.

6. Pharmaceutical Particulars

6.1 List of Excipients:
Starch
PVPK-30
Magnesium stearate

Purified Talc
Sodium Starch Glycolate
Cab-O-Sil
Easy Coat Fc Iron Oxide Yellow
Iso Propyl Alcohol
Methylene Dichloride

6.2 Incompatibilities:

Not Applicable

6.3 Shelf-life:

36 Months

6.4 Special precautions for storage:

Store in a cool (Below 30° C), and a Dry place. Protect from Light

6.5 Nature and contents of container:

Alu/Alu Blister pack of 10 tablets packed in a mono carton with pack insert, such 10 mono carton packed in one outer carton.

6.6 Special precautions for disposal

No special requirements

7. Marketing authorization holder and manufacturing site address

Medixperts Ltd
P.o box 40548_00100
KENYA

Manufactured by
Curis lifesciences Pvt. Limited
Pf-23 Sanand GIDC II, sanand-382110

8. Marketing authorization number

H2025/CTD12012/26446

9. Date of first registration/ renewal of the registration

27/08/2025

10. Date of Revision Of The Text

27/08/2025