Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Paralex MR

2. Qualitative and quantitative composition

Each film coated tablet contains Celecoxib 200mg, Paracetamol 500mg and Chlorzoxazone 250mg.

Excipients with known effect

Each tablet contains 10mg of lactose.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Tablet

A yellow color, oblong shape, biconvex film coated tablet bisected on one side

4. Clinical particulars

4.1 Therapeutic indications

Celecoxib is indicated in adults for the symptomatic relief in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis. Chlorzoxazone is a muscle relaxant which works by acting on the central nervous system. Paracetamol works by lowering the chemical substance (prostaglandins) in the body that causes pain.

4.2 Posology and method of administration

Adults and adolescents 16 years of age or older

The reommended dose for Paralex MR is one tablet taken twice daily.

Method of administration

Oral route

4.3 Contraindications

Celecoxib

Hypersensitivity to the active substance or to any of the excipients

Known hypersensitivity to sulfonamides.

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 inhibitors.

Paracetamol

Hypersensitivity to Paracetamol

Chlorzoxazone
Chlorzoxazone is contraindicated in any patient with a known or suspected intolerance or hypersensitivity to the drug or any of the product ingredients. If a sensitivity reaction such as urticaria, pruritus, or skin erythema occurs, discontinue chlorzoxazone. Angioedema or anaphylactic reactions are extremely rare.

4.4 Special warnings and precautions for use

Celecoxib

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 (CV) 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 bis in die (BID) and 400 mg 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).

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 totake 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 cando 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

Celecoxib

Anticoagulants

Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed (see section 4.4). Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin, some of them fatal.

Anti-hypertensives

NSAIDs may reduce the effect of anti-hypertensive medicinal products including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics or elderly patients) when ACE inhibitors, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including celecoxib (see section 4.4). Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted

in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients treated with placebo; this difference was statistically significant.

Ciclosporin and Tacrolimus

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

Acetylsalicylic acid

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see section 5.1).

Pharmacokinetic interactions

Effects of celecoxib on other medicinal products

CYP2D6 Inhibition

Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicinal products that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of medicinal products which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic medicinal products, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.

Concomitant administration of celecoxib 200 mg twice daily resulted in 2.6-fold and 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib inhibition of the CYP2D6 substrate metabolism.

CYP2C19 Inhibition

In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this in vitro finding is unknown. Examples of medicinal products which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate

In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two medicinal products.

Lithium

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 area under the curve (AUC) of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Oral contraceptives

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone /35 micrograms ethinylestradiol).

Glibenclamide/tolbutamide

Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.

Effects of other medicinal products on celecoxib

CYP2C9 Poor Metabolisers

In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers (see sections 4.2 and 5.2).

CYP2C9 Inhibitors and Inducers

Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib C_{max} of 60% and in AUC of 130%. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole and Antacids

Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

Paediatric population

Interaction studies have only been performed in adults.

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, respiratorydepression, coma, and death may result ifcoadministered. 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 Fertility, pregnancy, and lactation

Celecoxib:

Pregnancy

Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations. 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 ductus arteriosus 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. 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.

Chlorzoxazone & Paracetamol

Pregnancy
Pregnant women should exercise caution. It is advisable to consult a doctor before using it. Your doctor will prescribe only if the benefits outweigh the risks.
Breast feeding
Please consult your doctor before taking Chlorzoxazone & Paracetamol, your doctor will decide whether Chlorzoxazone & Paracetamolcan be taken by breastfeeding mothers or not.

4.7 Effects on ability to drive and use machines.
Patients who experience dizziness, vertigo or somnolence while taking Paralex MR should refrain from driving or operating machinery.

4.8 Undesirable effects
Celecoxib
Adverse reactions are listed by system organ class and ranked by frequency in **Table 1**, reflecting data from the following sources:

• Adverse reactions reported in osteoarthritis patients and rheumatoid arthritis patients at incidence rates greater than 0.01% and greater than those reported for placebo during 12 placebo- and/or active-controlled clinical trials of duration up to 12 weeks at celecoxib daily doses from 100 mg up to 800 mg. In additional studies using non-selective NSAID comparators, approximately 7400 arthritis patients have been treated with celecoxib at daily doses up to 800 mg, including approximately 2300 patients treated for 1 year or longer. The adverse reactions observed with celecoxib in these additional studies were consistent with those for osteoarthritis and rheumatoid arthritis patients listed in Table 1.

• Adverse reactions reported at incidence rates greater than placebo for subjects treated with celecoxib 400 mg daily in long-term polyp prevention trials of duration up to 3 years (the Adenoma Prevention with Celecoxib (APC) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials; see section 5.1, Cardiovascular safety – long-term studies involving patients with sporadic adenomatous polyps).

• Adverse drug reactions from post-marketing surveillance as spontaneously reported during a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). Even though these were identified as reactions from post- marketing reports, trial data was consulted to estimate frequency. Frequencies are based on a cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.

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

Adverse Drug Reaction Frequency						
System organ class	**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 available data)**
Infections and infestations		Sinusitis, upper respiratory tract infection, pharyngitis,urinary tract infection				
Blood and lymphatic system disorders			Anaemia	Leukopenia, thrombo-cytopenia	Pancytopenia[4]	
Immune system disorders		Hypersensitivity			Anaphylactic shock[4], anaphylactic reaction[4]	
Metabolism and nutrition disorders			Hyperkalaemia			
Psychiatric disorders		Insomnia	Anxiety, depression, fatigue	Confusional state, hallucinations[4]		
Nervous system disorders		Dizziness, hypertonia, headache[4]	Cerebral infarction[1], paraesthesia, somnolence	Ataxia, dysgeusia	Haemorrhage intracranial (including fatal intracranial haemorrhage)[4], meningitis aseptic[4], epilepsy (including aggravated epilepsy)[4], ageusia[4], anosmia[4]	
Eye disorders			Vision blurred, conjunctivitis[4]	Eye haemorrhage[4]	Retinal artery occlusion[4], retinal vein occlusion[4]	
Ear and labyrinth disorders			Tinnitus, hypoacusis[1]			
Cardiac disorders		Myocardial infarction[1]	Cardiac failure, palpitations, tachycardia	Arrhythmia[4]		
Vascular disorders	Hypertension[1] (including aggravated hypertension)			Pulmonary embolism[4], flushing[4]	Vasculitis[4]	
Respiratory, thoracic, and mediastinal disorders		Rhinitis, cough, dyspnoea[1]	Bronchospasm[4]	Pneumonitis[4]		
Gastrointestinal disorders		Nausea[4], abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1], dysphagia[1]	Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal	Gastro-intestinal haemorrhage[4], duodenal ulcer, gastric ulcer, oesophageal ulcer,		

			inflammation), eructation	intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, pancreatitis, colitis[4]		
Hepatobiliary disorders			Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT)	Hepatitis[4]	Hepatic failure[4] (sometimes fatal or requiring liver transplant), hepatitis fulminant[4] (some with fatal outcome), hepatic necrosis[4], cholestasis[4], hepatitis cholestatic[4], jaundice[4]	
Skin and subcutaneous tissue disorders		Rash, pruritus (includes pruritus generalised)	Urticaria, ecchymosis[4]	Angioedema[4], alopecia, photo-sensitivity	Dermatitis exfoliative[4], erythema multiforme[4], Stevens-Johnson syndrome[4], toxic epidermal necrolysis[4], drug reaction with eosinophilia and systemic symptoms (DRESS)[4], acute generalised exanthematous pustulosis (AGEP)[4], dermatitis bullous[4]	
Musculoskeletal and connective tissue disorders		Arthralgia[4]	Muscle spasms (leg cramps)		Myositis[4]	
Renal and urinary disorders			Blood creatinine increased, blood urea increased	Renal failure acute[4], hypo-natraemia[4]	Tubulointerstitial nephritis[4], nephrotic syndrome[4], glomerulonephritis minimal lesion[4]	
Reproductive system and breast disorders				Menstrual disorder[4]		Infertility female (female fertility decreased)[3]
General disorders and		Influenza-like illness, oedema	Face oedema, chest pain[4]			

administrative site conditions		peripheral/ fluid retention				
Injury, poisoning and procedural complications		Injury (accidental injury)				

SGOT - serum glutamic oxaloacetic transaminase
SGPT - serum glutamic pyruvic transaminase
[1] Adverse drug reactions that occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials). The adverse drug reactions listed above for the polyp prevention trials are only those that have been previously recognised in the post-marketing surveillance experience,or have occurred more frequently than in the arthritis trials.
[2] Furthermore, the following *previously unknown* adverse reactions occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials):
Common: angina pectoris, irritable bowel syndrome, nephrolithiasis, blood creatinine increased, benign prostatic hyperplasia, weight increased. **Uncommon:** helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection, lipoma, vitreous floaters, conjunctival haemorrhage, deep vein thrombosis, dysphonia, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, allergic dermatitis, ganglion, nocturia, vaginal haemorrhage, breast tenderness, lower limb fracture, blood sodium increased.
[3] Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable.
[4] Frequencies are based on cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.

In final data (adjudicated) from the APC and PreSAP trials in patients treated with celecoxib 400 mg daily for up to 3 years (pooled data from both trials; see section 5.1 for results from individual trials), the excess rate over placebo for myocardial infarction was 7.6 events per 1,000 patients (uncommon) and there was no excess rate for stroke (types not differentiated) over placebo.

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

4.9 Overdose

It is generally prescribed for short-term use. Avoid taking PARALEX MR for longer durations unless prescribed by the doctor, which could lead to unpleasant side-effects. Long-term use of PARALEX MR could lead to kidney damage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

CELECOXIB

Celecoxib inhibits cyclooxygenase 2 (COX-2) enzyme, reducing pain and inflammation. It is important to note that though the risk of bleeding with celecoxib is lower than with certain other NSAIDS, it exists nonetheless and caution must be observed when it is administered to those with a high risk of gastrointestinal bleeding.

Mechanism of action

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-phosphoinositidedependent 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

Animal and clinical studies have determined that acetaminophen has both antipyretic and analgesic effects. This drug has been shown to lack anti-inflammatory effects. As opposed to the salicylate drug class, acetaminophen does not disrupt tubular secretion of uric acid and does not affect acid-base balance if taken at the recommended doses. Acetaminophen does not disrupt hemostasis and does not have

inhibitory activities against platelet aggregation. Allergic reactions are rare occurrences following acetaminophen use.

Mechanism of action

According to its FDA labeling, acetaminophen's exact mechanism of action has not been fully established Label - despite this, it is often categorized alongside NSAIDs (nonsteroidal antiinflammatory drugs) due to its ability to inhibit the cyclooxygenase (COX) pathways. It is thought to exert central actions which ultimately lead to the alleviation of pain symptoms. One theory is that acetaminophen increases the pain threshold by inhibiting two isoforms of cyclooxygenase, COX-1 and COX-2, which are involved in prostaglandin (PG) synthesis. Prostaglandins are responsible for eliciting pain sensations. Acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, therefore, has no peripheral anti-inflammatory effects. Though acetylsalicylic acid (aspirin) is an irreversible inhibitor of COX and directly blocks the active site of this enzyme, studies have shown that acetaminophen (paracetamol) blocks COX indirectly. Studies also suggest that acetaminophen selectively blocks a variant type of the COX enzyme that is unique from the known variants COX-1 and COX-2. This enzyme has been referred to as COX-3. The antipyretic actions of acetaminophen are likely attributed to direct action on heat-regulating centers in the brain, resulting in peripheral vasodilation, sweating, and loss of body heat. The exact mechanism of action of this drug is not fully understood at this time, but future research may contribute to deeper knowledge.

CHLORZOXAZONE

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal conditions. Data available from animal experiments as well as human study indicate that chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex a.c. 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.

Mechanism of action

Chlorzoxazone inhibits degranulation of mast cells, subsequently preventing the release of histamine and slow-reacting substance of anaphylaxis (SRS-A), mediators of type I allergic reactions. Chlorzoxazone also may reduce the release of inflammatory leukotrienes. Chlorzoxazone may act by inhibiting calcium and potassium influx which would lead to neuronal inhibition and muscle relaxation. Data available from animal experiments as well as human study indicate that 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.

5.2 Pharmacokinetic properties

CELECOXIB

Absorption

Celecoxib is absorbed rapidly in the gastrointestinal tract. When a single oral dose of 200 mg was given to healthy research subjects, the peak plasma levels of celecoxib occurred within 3 hours. The Cmax is 705 ng/mL. When multiple doses are given, steady-state concentrations are reached on or before day. When taken with a high-fat meal, peak plasma levels are delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%.31 The AUC of celecoxib has been shown to be significantly lower in patients with chronic renal impairment. A meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC (area under the curve) of celecoxib in black patients compared to Caucasians for unknown reasons.

Distribution

The apparent volume of distribution of celecoxib at steady state (Vss/F) is about 429 L25, which suggests wide distribution into various tissues. Celecoxib is not preferentially bound to red blood cells. Another resource reports a volume of distribution of 455 ± 166L.

Route of elimination

Celecoxib is primarily eliminated by hepatic metabolism with small amounts (<3%) of the unchanged drug found in both the urine and feces. About 57% of an oral dose of celecoxib is excreted in the feces and 27% is found to be excreted into the urine in the form of metabolites.

The main metabolite in urine and feces is identified as the carboxylic acid metabolite (73%). The amount of glucuronide in the urine is reported to be low.

PARACETAMOL

Absorption

Acetaminophen has 88% oral bioavailability and reaches its highest plasma concentration 90 minutes after ingestion. Peak blood levels of free acetaminophen are not reached until 3 hours after rectal administration of the suppository form of acetaminophen and the peak blood concentration is approximately 50% of the observed concentration after the ingestion of an equivalent oral dose (10-20 mcg/mL). The percentage of a systemically absorbed rectal dose of acetaminophen is inconsistent, demonstrated by major differences in the bioavailability of acetaminophen after a dose administered rectally. Higher rectal doses or an increased frequency of administration may be used to attain blood concentrations of acetaminophen similar to those attained after oral acetaminophen administration.

Distribution

Volume of distribution is about 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. Acetaminophen appears to be widely distributed throughout most body tissues except in fat.

Route of elimination

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as free (unconjugated) acetaminophen and at least 90% of the administered dose is excreted within 24 hours.

CHLORZOXAZONE

Metabolism

Chlorzoxazone is rapidly metabolized in the liver and is excreted in the urine, primarily in a conjugated form as the glucuronide.

Route of elimination

Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide.

Toxicity

Oral, mouse: LD50 = 440 mg/kg; Oral, rat: LD50 = 763 mg/kg; Symptoms of overdose include diarrhea, dizziness, drowsiness, headache, light-headedness, nausea, and vomiting.

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

Lactose
Isopropyl alcohol
Microcrystalline Cellulose
PVPK Povidone
Cross povidone
Potassium Polacrillin
Talcum
Magnesium Stearate
Colloidal Sillicon Dioxide Light
Hydroxypropyl Methyl Cellulose
Poly Ethylene Glycol
Ferric Oxide Yellow
Titanium Dioxide

6.2 Incompatibilities

None known

6.3 Shelf life

36 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

1X10 Tablet Alu Alu Blister

6.6 Special precautions for disposal and other handling:

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
DUOLIFE PHARMACEUTICALS
Manufacturing site address:
4 CARE LIFESCIENCE PVT. LTD.
Survey no. 23/3P & 24, opp. Jeans factory,
Daduramvistar, village- Bagdol. Tal. Kathlal,
Dist. Kheda-387630, Gujarat, India.

8. Marketing authorization number
H2024/CTD10545/23379

9. Date of first registration
28/02/2024

10. Date of revision of the text:
November 2024