Professional Information

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

PARECOXIB 40 MACLEODS; 40 mg IV/IM powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 40 mg parecoxib (as 42,36 mg parecoxib sodium).

After reconstitution with 2 mL sodium chloride intravenous infusion (0,9 % *m/v*), the concentration of parecoxib is 20 mg/mL.

Excipient with known effect:

PARECOXIB 40 MACLEODS contains less than 1 mmol sodium (23 mg) per dose.

When reconstituted in sodium chloride solution (0,9 % *m/v*), PARECOXIB 40 MACLEODS injection contains approximately 0,44 mmol/L of sodium per vial.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to off-white lyophilised cake or powder in a single-use glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term management of post-operative pain in patients who need parenteral therapy and for when a similar benefit could not be obtained from oral therapy. Patients should be transferred to alternative oral therapy as soon as clinically indicated.

PARECOXIB 40 MACLEODS is also indicated for the reduction of post-operative opioid use for up to 48 hours in patients who have undergone hip replacement surgery.

4.2 Posology and method of administration

Posology

PARECOXIB 40 MACLEODS is only indicated for patients with a need for parenteral therapy and for whom a similar benefit could not be obtained from alternative oral therapy. It is recommended that patients be transitioned to alternative oral therapy as soon as clinically indicated.

As the cardiovascular risk of PARECOXIB 40 MACLEODS may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. However, the relevance of these findings for the short-term use of PARECOXIB 40 MACLEODS in the post-operative setting has not been evaluated.

Management of post-operative pain

The usual recommended dose is a single or initial 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle. When given at the recommended doses for management of acute pain, the onset of analgesia was 7 – 14 minutes and reached a peak effect within 2 hours. After a single dose, the duration of analgesia was dose and clinical pain model dependent and ranged from 7 to greater than 24 hours.

Concomitant use with opioid analgesia

Opioid analgesia can be used concurrently with PARECOXIB 40 MACLEODS dosing as described in the paragraph above, for the management of post-operative pain for up to 48 hours. In a hip replacement surgery trial, the daily requirements for opioid were reduced by 20 to 40 % when co-administered with PARECOXIB 40 MACLEODS. An optimal effect is

achieved when PARECOXIB 40 MACLEODS is given at the end of hip replacement surgery, prior to opioid administration. In all clinical assessments, PARECOXIB 40 MACLEODS was administered at a fixed time interval (i.e. 12 hourly), whereas the opioids were administered when needed (PRN basis).

Special populations

Elderly population

Dosage adjustment in the elderly is not generally necessary. However, for elderly female patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of PARECOXIB 40 MACLEODS injection and reduce the maximum daily dose to 40 mg.

Hepatic impairment

No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh scale 5 – 6). Introduce PARECOXIB 40 MACLEODS injection with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh scale 7 – 9) and reduce the maximum daily dose to 40 mg. Patients with severe hepatic impairment (Child-Pugh scale > 9) should not be given PARECOXIB 40 MACLEODS (see section 4.3).

Renal impairment

On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate (creatinine clearance of 30 – 80 mL/min) renal impairment. In patients with severe (creatinine clearance < 30 mL/min) renal impairment or patients who may be predisposed to fluid retention, PARECOXIB 40 MACLEODS should not be used (see section 4.3).

Paediatric population

PARECOXIB 40 MACLEODS injection has not been studied in patients under 18 years old. Therefore, its use is not recommended in these patients.

Method of administration

For intravenous or intramuscular injection.

For instructions on PARECOXIB 40 MACLEODS reconstitution, before administration of injection and PARECOXIB 40 MACLEODS diluent incompatibilities, refer to sections 6.2 and 6.6.

4.3 Contraindications

- Hypersensitivity to parecoxib or to any of the excipients of PARECOXIB 40 MACLEODS (listed in section 6.1)
- History of hypersensitivity to sulphonamides
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAID) or other cyclooxygenase-2 (COX-2) specific inhibitors
- Severe impairment of hepatic function
- Severe renal impairment
- Post- and peri-operative analgesia in the setting of coronary artery bypass surgery (CABG)
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease
- History of gastrointestinal perforation, ulceration or bleedings (PUBs) related to previous NSAIDs, including PARECOXIB 40 MACLEODS
- Active or history of recurrent ulcer/haemorrhage/perforations
- Concomitant therapy with lithium or digoxin
- Porphyria
- Pregnancy and lactation (see section 4.6)
- Children younger than 18 years of age.

4.4 Special warnings and precautions for use

PARECOXIB 40 MACLEODS may predispose to cardiovascular events, cerebrovascular events, gastrointestinal events or cutaneous reactions which may be fatal.

Administration other than IV or IM

Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.

Hypersensitivity reactions

Hypersensitivity reactions such as anaphylaxis and angioedema have been reported in post-marketing experience with parecoxib as in PARECOXIB 40 MACLEODS injection. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3).

Cardiovascular effects

PARECOXIB 40 MACLEODS has been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long-term. The magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy been associated with increased risk.

Two separate published studies on coronary artery bypass graft (CABG) surgery showed that patients receiving parecoxib for a minimum of 3 days followed by valdecoxib (the active metabolite of parecoxib) for 7 – 14 days, had increased incidence of cardiovascular/thromboembolic events (e.g. myocardial infarction and cerebrovascular accident) compared to those receiving placebo. This risk is associated with higher doses and prolonged duration of treatment (see section 4.3).

Caution is advised when PARECOXIB 40 MACLEODS is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes mellitus, smoking and hypercholesterolaemia. Appropriate measures should be taken and discontinuation of

PARECOXIB 40 MACLEODS therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Hypertension

PARECOXIB 40 MACLEODS can lead to the onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including PARECOXIB 40 MACLEODS, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with PARECOXIB 40 MACLEODS and throughout the course of therapy.

If blood pressure rises significantly, alternative treatment should be considered.

Gastrointestinal (GI) effects

Upper gastrointestinal (GI) complications including perforations, ulcers, or bleedings, some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with PARECOXIB 40 MACLEODS: the elderly, patients with cardiovascular disease, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, selective serotonin reuptake inhibitors or patients with a prior history of gastrointestinal disease, such as ulceration, GI bleeding, inflammatory conditions (including ulcerative colitis or Crohn's disease), hiatus hernia, gastro-oesophageal reflux disease or angiodysplasia which may be exacerbated. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when PARECOXIB 40 MACLEODS is taken concomitantly with acetylsalicylic acid (aspirin) (even at low doses).

When gastrointestinal bleeding or ulceration occurs in patients receiving PARECOXIB 40 MACLEODS, treatment with PARECOXIB 40 MACLEODS should be discontinued.

Skin reactions

Serious skin reactions which may be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in post-marketing experience with parecoxib. PARECOXIB 40 MACLEODS injection should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

DRESS syndrome may occur with PARECOXIB 40 MACLEODS exposure, based on other serious skin reactions reported with celecoxib and valdecoxib exposure. 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.

Appropriate measures should be taken by medical practitioners to monitor for any serious skin reactions with therapy, e.g. additional patient consultations. Patients should be advised to immediately report any emergent skin condition to their medical practitioner.

Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors.

Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see section 4.3). Patients without a history of sulphonamide allergy may also be at risk for serious skin reactions.

Renal and hepatic effects

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib as in PARECOXIB 40 MACLEODS (see section 4.8).

PARECOXIB 40 MACLEODS injection should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or severe hepatic impairment (Child-Pugh scale ≥ 9) (see section 4.3).

Caution should be used when initiating treatment with PARECOXIB 40 MACLEODS injection in patients with moderate hepatic impairment (Child-Pugh scale 7 – 9), and in

patients with any form of dehydration. It is advisable to rehydrate patients first and then start therapy with PARECOXIB 40 MACLEODS injection.

Fluid retention and oedema

Due to inhibition of prostaglandin synthesis, fluid retention and oedema may occur in patients taking PARECOXIB 40 MACLEODS; therefore, PARECOXIB 40 MACLEODS should not be used in patients with compromised cardiac function, pre-existing oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolaemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored (see section 4.3).

Aspirin and other NSAIDs

Because of its lack of platelet aggregation effects, PARECOXIB 40 MACLEODS is not a substitute for aspirin for prophylaxis of cardiovascular disease. Therefore, antiplatelet therapies should not be discontinued.

The concomitant use of PARECOXIB 40 MACLEODS injection with other non-specific NSAIDs should be avoided.

Warfarin and other oral anticoagulants

Caution should be exercised when co-administering PARECOXIB 40 MACLEODS with warfarin and other oral anticoagulants (see section 4.5).

Concomitant use of PARECOXIB 40 MACLEODS with other anticoagulant medicines may increase the risk of intra- and post- operative bleeding.

Severe hypotension

Cases of severe hypotension shortly after parecoxib administration have been reported. Some of these cases have occurred without other signs of anaphylaxis. The medical practitioner should be prepared to treat severe hypotension.

General

PARECOXIB 40 MACLEODS may mask fever and other signs of inflammation.

Caution should also be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving PARECOXIB 40 MACLEODS injection.

Safety and efficacy of PARECOXIB 40 MACLEODS injection has not been established for periods of use exceeding 96 hours.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per mL and is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

General

In vitro studies with human hepatic microsomal systems reported no significant inhibitory effects on CYP3A4, 2D6, 2E1, and 1A2 isoforms by parecoxib as in PARECOXIB 40 MACLEODS or valdecoxib. Weak inhibitory activity was reported for 2C9 and 2C19 isozymes.

PARECOXIB 40 MACLEODS is hydrolysed to the active substance valdecoxib. In humans, studies reported that valdecoxib metabolism is predominantly mediated via cytochrome P450 CYP3A4 and 2C9 isozymes. Glucuronidation is a further route of metabolism. The alternate CYP-mediated and non-CYP-mediated metabolic pathways may reduce the likelihood of individuals with genetic polymorphisms having substantially higher plasma concentrations due to impaired metabolism.

Effect of other medicines on PARECOXIB 40 MACLEODS

Fluconazole and ketoconazole

Plasma exposure (AUC and C_{max}) to valdecoxib increases (62 % and 19 %, respectively) when co-administered with fluconazole.

The dose of PARECOXIB 40 MACLEODS injection should be reduced in patients receiving fluconazole therapy.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38 % and 24 %, respectively) when co-administered with ketoconazole; however, a dosage adjustment may not be necessary for patients receiving ketoconazole.

Effect of PARECOXIB 40 MACLEODS on other medicines

Aspirin

Parecoxib injection had no effect on aspirin-mediated inhibition of platelet aggregation or bleeding times in volunteers. Clinical studies reported that parecoxib injection can be given with low dose aspirin (≤ 325 mg).

Because of its lack of platelet aggregation effects, PARECOXIB 40 MACLEODS injection is not a substitute for aspirin for prophylaxis of cardiovascular disease. There is no evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with PARECOXIB 40 MACLEODS.

Warfarin or similar medicines

Anticoagulant therapy should be more frequently monitored, particularly during the first few days after initiating PARECOXIB 40 MACLEODS injection therapy in patients receiving warfarin or similar medicines, since these patients have an increased risk of bleeding complications.

ACE inhibitors

Inhibition of prostaglandins may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients receiving PARECOXIB 40 MACLEODS concomitantly with ACE inhibitors.

In patients who are elderly, volume-depleted (including those on diuretic therapy) or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors such as PARECOXIB 40 MACLEODS, with ACE inhibitors or angiotensin-II antagonists, may result in deterioration of renal function, including possible acute renal failure. These effects may be reversible.

Ciclosporin or tacrolimus

Co-administration of PARECOXIB 40 MACLEODS and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. Renal function should be monitored when PARECOXIB 40 MACLEODS injection and any of these medicines are co-administered.

Diuretics

PARECOXIB 40 MACLEODS may reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

Lithium

PARECOXIB 40 MACLEODS produces significant decreases in lithium serum clearance (25 %) and renal clearance (30 %) with a 34 % higher serum exposure compared to lithium alone (see section 4.3).

Other

Parecoxib did not produce clinically relevant inhibition of the CYP2D6-mediated pathway involved in the conversion of dextromethorphan to dextrorphan.

Co-administration of parecoxib with glibenclamide (CYP3A4 substrate) did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

PARECOXIB 40 MACLEODS may be co-administered with opioid analgesics.

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate, parecoxib did not have a clinically significant effect on the plasma exposure to methotrexate.

Injectable anaesthetics

Co-administration of IV parecoxib injection 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics of IV propofol or IV midazolam. Additionally, co-

administration with IV parecoxib injection had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics

In a post-orthopaedic surgery study in which parecoxib injection was administered preoperatively, no evidence of medicine interaction was observed in patients receiving parecoxib injection and the inhalation anaesthetic medicines nitrous oxide and isoflurane.

4.6 Fertility, pregnancy and lactation

Safety of PARECOXIB 40 MACLEODS has not been demonstrated in pregnancy and lactation. PARECOXIB 40 MACLEODS is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

Cases of adverse reactions in the foetus or newborn have been reported with exposure to the NSAID class of medicine during pregnancy.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

From the 20th week of pregnancy onward, the use of PARECOXIB 40 MACLEODS may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Foetal 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 upon discontinuation of the NSAID treatment.
- Cardiopulmonary toxicity: Premature constriction/closure of the foetal ductus arteriosus *in utero*, and possibly, persistent pulmonary hypertension of the newborn with regular use of NSAID treatment during pregnancy.

At the end of pregnancy, the mother and neonate may be exposed to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- The onset of labour may be delayed and its duration increased due to inhibition of uterine contractions.

Consequently, PARECOXIB 40 MACLEODS should not be used during pregnancy.

Breastfeeding

Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1 % of the weight-adjusted maternal dose). Women breastfeeding their infants should not be given PARECOXIB 40 MACLEODS.

Fertility

The use of this medicine, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. Based on the mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including PARECOXIB 40 MACLEODS, should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence after receiving PARECOXIB 40 MACLEODS should refrain from driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction for PARECOXIB 40 MACLEODS is nausea. The most serious reactions occur less frequently and include cardiovascular events such as myocardial infarction and severe hypotension, as well as hypersensitivity events such as anaphylaxis, angioedema and severe skin reactions. Following coronary artery bypass graft surgery, patients administered parecoxib had a higher risk of adverse reactions such as: cardiovascular/thromboembolic events (including myocardial infarction, stroke/TIA, pulmonary embolus, and deep vein thrombosis; see sections 4.3 and 5.1), deep surgical infections, and sternal wound healing complications.

Tabulated summary of adverse reactions

The following side effects have been reported in patients on PARECOXIB 40 MACLEODS treatment.

System organ class/Frequency	**Undesirable effects**
Infections and infestations	
Frequent	Alveolar osteitis (dry socket)
Less frequent	Abnormal sternal serous wound drainage, wound infection, pharyngitis
Blood and lymphatic system disorders	
Frequent	Post-operative anaemia
Less frequent	Thrombocytopenia
Immune system disorders	
Less frequent	Anaphylactoid reaction

Frequency unknown	Hypersensitivity reactions including anaphylaxis, angioedema
Metabolism and nutrition disorders	
Frequent	Hypokalaemia
Less frequent	Hyperglycaemia, anorexia
Psychiatric disorders	
Frequent	Insomnia
Less frequent	Agitation
Nervous system disorders	
Frequent	Hypoaesthesia, dizziness
Less frequent	Cerebrovascular disorder
Ear and labyrinth disorders	
Less frequent	Earache
Cardiac disorders	
Less frequent	Myocardial infarction, bradycardia, dysrhythmia, palpitations, cardiovascular thrombotic events, tachycardia, congestive heart failure
Frequency unknown	Circulatory collapse
Vascular disorders	
Frequent	Hypotension
Less frequent	Aggravated hypertension, postural hypotension, hypertension
Respiratory, thoracic and mediastinal	
Frequent	Respiratory insufficiency
Less frequent	Pulmonary embolism
Frequency unknown	Dyspnoea
Gastrointestinal disorders	
Frequent	Nausea, abdominal pain, vomiting, constipation, dyspepsia

Less frequent	Gastroduodenal ulceration, gastroesophageal reflux disease, dry mouth, abnormal gastrointestinal sounds, pancreatitis, oesophagitis, oedema mouth (perioral swelling), flatulence
Skin and subcutaneous tissue disorders	
Frequent	Pruritus, hyperhidrosis
Less frequent	Ecchymosis, rash, urticaria
Frequency unknown	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Less frequent	Back pain, arthralgia
Renal and urinary disorders	
Frequent	Oliguria
Less frequent	Acute renal failure
Frequency unknown	Renal failure
General disorders and administration site conditions	
Frequent	Peripheral oedema
Less frequent	Asthenia, injection site pain, injection site reaction
Investigations	
Less frequent	Increased blood creatinine, increased creatine phosphokinase, increased LDH, increased SGOT, increased SGPT, increased BUN
Injury, poisoning and procedural complications	
Less frequent	Post-operative skin complications

Description of selected adverse reactions

In post-marketing experience, toxic epidermal necrolysis has been reported in association with the use of valdecoxib and cannot be ruled out for parecoxib as in PARECOXIB 40 MACLEODS (see section 4.4). Circulatory collapse, erythema multiforme, Stevens-

Johnson syndrome, toxic epidermal necrolysis, renal failure, acute renal failure and hypersensitivity reactions including anaphylaxis and angioedema have been reported. In addition, the following rare, serious adverse reactions have been reported in association with the use of NSAIDs and cannot be ruled out for PARECOXIB 40 MACLEODS: bronchospasm and hepatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

In case of overdose, patients should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, Coxibs, ATC code: M01AH04

Parecoxib sodium, a COX-2 selective non-steroidal anti-inflammatory drug (NSAID), is an inactive prodrug of valdecoxib. Following injection, parecoxib is rapidly hydrolysed to valdecoxib, which is active in animal models of prostaglandin-dependent pain, inflammation and fever. The mechanism of action of valdecoxib is predominantly by inhibition of COX-2-

mediated prostaglandin synthesis. At therapeutic doses, valdecoxib is a specific COX-2 inhibitor and does not inhibit COX-1.

5.2 Pharmacokinetic properties

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacological moiety, by enzymatic hydrolysis in the liver.

Absorption

Exposure of valdecoxib following single doses of parecoxib injection, as measured by both the area under the plasma concentration vs. time curve (AUC) and peak concentration (C_{max}), is approximately linear in the range of clinical doses. AUC and C_{max} following twice a day (BID) administration of valdecoxib is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with BID dosing.

Following single IV and IM doses of parecoxib sodium 20 mg, C_{max} of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C_{max} following IV and IM administration.

Distribution

The volume of distribution of valdecoxib after its IV administration is approximately 55 L. Plasma protein binding is approximately 98 % over the concentration range achieved with the highest recommended dose, 80 mg/day. Valdecoxib, but not parecoxib, is extensively partitioned into erythrocytes.

Biotransformation

Parecoxib is rapidly and almost completely converted to valdecoxib in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P450 CYP3A4 and CYP2C9 isoenzymes and CYP-independent glucuronidation of the sulphonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10 % of the

concentration of valdecoxib; but because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium. The valdecoxib metabolite undergoes extensive metabolism, with less than 5 % of the dose excreted in urine and faeces.

Elimination

Valdecoxib is eliminated via hepatic metabolism with less than 5 % unchanged medicine recovered in the urine. No unchanged parecoxib is detected in urine and only trace amounts in the faeces. About 70 % of the dose is excreted in the urine as inactive metabolites. Plasma clearance (CLp) for valdecoxib is about 6 L/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life ($t_{½}$) of valdecoxib is about 8 hours.

Special populations

Elderly

In healthy elderly subjects, the apparent clearance of valdecoxib after oral intake was reduced, resulting in an approximately 40 % higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted for body weight, steady state plasma exposure of valdecoxib was 16 % higher in elderly females compared to elderly males.

Renal impairment

In patients with varying degrees of renal impairment administered 20 mg IV parecoxib injection as a single dose, parecoxib was rapidly cleared from plasma. No changes in valdecoxib clearance were found even in patients with renal impairment. Dosages of more than 20 mg have not been studied in renal impairment. Therefore, on the basis of pharmacokinetics, dosing adjustment in patients with mild to moderate impaired renal function is not necessary.

Hepatic impairment

Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh scale 7 – 9), treatment should be initiated with half the usual recommended dose of parecoxib

injection and the maximum daily dose should be reduced to 40 mg since valdecoxib exposures were more than doubled (130 %) in these patients. Patients with severe hepatic impairment have not been studied and therefore the use of parecoxib injection in patients with severe hepatic impairment is not recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic sodium phosphate

Phosphoric acid and/or sodium hydroxide (if required for pH adjustment)

6.2 Incompatibilities

PARECOXIB 40 MACLEODS must not be mixed with other medicinal products except for those mentioned in section 6.6.

Use of sterile water for injection is **not recommended**, as the resulting solution is not isotonic.

PARECOXIB 40 MACLEODS and opioids should not be administered together in the same syringe.

PARECOXIB 40 MACLEODS should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after PARECOXIB 40 MACLEODS injection with a solution of known compatibility (see section 6.6).

Use of lactated Ringer's or 5 % glucose in lactated Ringer's for reconstitution will cause the active substance to precipitate from solution and therefore is **not recommended**.

6.3 Shelf-life

The shelf-life of the product is 24 months before reconstitution.

After reconstitution:

Reconstituted solution should be stored in the vial at or below 25 °C and used within 24 hours. Do not store in a refrigerator or freezer.

However, due to the importance of microbiological infection risk for injectable products without preservatives, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. In-use storage times must not normally be longer than 12 hours at 25 °C.

6.4 Special precautions for storage

Store at or below 30 °C in the outer container in order to protect from light.

6.5 Nature and contents of container

PARECOXIB 40 MACLEODS lyophilised powder is packed in a 5 mL colourless Type I single use glass vial, sealed with a chlorinated butyl rubber stopper coated with ETFE (ethylene tetrafluoroethylene) with an aluminium-plastic cap.

Pack sizes available: sets of either 1, 3, 5 or 10 vials containing parecoxib 40 mg (as parecoxib sodium) packed into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitute PARECOXIB 40 MACLEODS injection with 2 mL (40 mg vials) sodium chloride solution (0,9 % *m/v*) using aseptic technique. The only other acceptable solvents for reconstitution are 5 % glucose intravenous infusion, 0,45 % sodium chloride and 5 % glucose injection.

The reconstituted solution is clear and colourless.

After reconstitution, PARECOXIB 40 MACLEODS injection should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

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8. REGISTRATION NUMBER

57/2.9/0737.736

9. DATE OF FIRST AUTHORISATION

Date of registration: 09 September 2025

10. DATE OF REVISION OF TEXT

Not applicable.