PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PERICOB 40 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, the concentration of parecoxib is 20 mg/ml. Each 2 ml of reconstituted powder contains 40 mg of parecoxib.

Sugar free.

When reconstituted in sodium chloride solution (0,9 % w/v), PERICOB 40 Injection contains approximately 0,44 mmol/L of sodium per 40 mg vial.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection.

PERICOB 40 vial: White to off-white, lyophilised powder in a single use 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. It is reminded that patients be transferred to alternative oral therapy as soon as clinically indicated.

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

4.2 Posology and method of administration

Posology

PERICOB 40 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 PERICOB 40 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 PERICOB 40 in the post-operative setting has not been evaluated.

Safety and efficacy of PERICOB 40 have not been established for periods of use exceeding 96 hours.

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. 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 PERICOB 40 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 significantly reduced (20 - 40 %) when co-administered with PERICOB 40. An optimal effect is achieved when PERICOB 40 is given at the end of hip replacement surgery, prior to opioid administration. In all clinical assessments PERICOB 40 was administered at a fixed time interval (i.e. 12 hourly), whereas

the opioids were administered when needed (PRN basis).

Special populations

Elderly

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 PERICOB 40 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 PERICOB 40 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. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh scale > 9); therefore, its use is not recommended in these patients (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, PERICOB 40 should not be used (see section 4.3).

Children

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

Method of administration

PERICOB 40 can be administered intravenously (IV) or intramuscularly (IM). 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. For instructions on reconstitution of PERICOB 40 before administration and PERICOB 40 diluent incompatibilities, see sections 6.2 and 6.6.

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

4.3 Contraindications

- Hypersensitivity to parecoxib or to any of the excipients (see section 6.1).
- History of previous serious allergic medicine reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulfonamides (see sections 4.4 and 4.8).
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or nonsteroidal anti-inflammatory medicines (NSAIDs) including COX-2 inhibitors.
- Pregnancy and lactation (see section 4.6).
- Severe hepatic impairment (serum albumin < 25 g/l or Child-Pugh score ≥10).
- Severe renal impairment.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Treatment of post-operative pain following coronary artery bypass graft (CABG) surgery (see sections 4.8 and 5.1).
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.
- Children younger than 18 years.

4.4 Special warnings and precautions for use

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

During pregnancy, the regular use of non-steroidal inflammatory parecoxib may result in:

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period

Second and Third trimester.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

Parecoxib reaction with Eosinophillia and Systemic Symptoms (DRESS) has been

reported in patients taking NSAIDs such as PERICOB 40. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue PERICOB 40 and evaluate the patient immediately.

Cardiovascular

There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment. 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.

Caution is advised when PERICOB 40 is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia (see section 5.1).

Appropriate measures should be taken and discontinuation of PERICOB 40 therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Acetylsalicylic acid (aspirin) and other NSAIDs

Because of its lack of platelet effects, PERICOB 40 is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, antiplatelet therapies should not be discontinued (see section 5.1). Caution should be exercised when co-

administering PERICOB 40 with warfarin and other oral anticoagulants (see section 4.5). The concomitant use of PERICOB 40 with other non- acetylsalicylic acid NSAIDs should be avoided.

PERICOB 40 may mask fever and other signs of inflammation (see section 5.1).

In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with PERICOB 40. Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving PERICOB 40.

Gastrointestinal

Upper gastrointestinal (GI) complications (perforations, ulcers or bleedings [PUBs]), 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 NSAIDs; the elderly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding, or patients using acetylsalicylic acid concomitantly. The NSAIDs class is also associated with increased GI complications when co-administered with glucocorticoids, selective serotonin reuptake inhibitors, other antiplatelet medicines, other NSAIDs or patients ingesting alcohol. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is used concomitantly with acetylsalicylic acid (even at low doses).

Skin reactions

Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib, as contained in PERICOB 40. Additionally, fatal reports of toxic epidermal necrolysis have been

reported through post-marketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib (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. Appropriate measures should be taken by doctors 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 doctor.

PERICOB 40 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. 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 sulfonamide allergy may be at greater risk of skin reactions (see section 4.3). Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity

Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulfonamides (see section 4.3). PERICOB 40 should be discontinued at the first sign of hypersensitivity.

Cases of severe hypotension shortly following parecoxib administration have been reported in post-marketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The doctor should be prepared to treat severe hypotension.

Fluid retention, oedema, renal

Due to inhibitors of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking parecoxib, therefore PERICOB 40 should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of PERICOB 40 should be taken.

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib (see section 4.8). Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering PERICOB 40 in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with PERICOB 40 in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with PERICOB 40.

Hypertension

PERICOB 40 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. PERICOB 40 should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with PERICOB 40 and throughout the course of therapy. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic impairment

PERICOB 40 should be used with caution in patients with moderate hepatic impairment (Child-Pugh score 7-9) (see section 4.2).

Use with oral anticoagulants

The concomitant use of NSAIDs, including PERICOB 40 with oral anticoagulants increases the risk of bleeding. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban) (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

PERICOB 40 is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of platelet effects.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with PERICOB 40.

Pharmacodynamic interactions

Anticoagulant therapy should be monitored, particularly during the first few days after initiating PERICOB 40 therapy 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 PERICOB 40 is initiated or the dose of PERICOB 40 is changed (see section 4.4).

PERICOB 40 had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that PERICOB 40 can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as

with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see section 5.1).

Co-administration of parecoxib and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

Inhibition of prostaglandins by NSAIDs, including COX-2 inhibitors, may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers, and diuretics. This interaction should be given consideration in patients receiving PERICOB 40 concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers, and diuretics.

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, with ACE inhibitors or Angiotensin-II antagonists, may result in further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Therefore, the concomitant administration of these medicines should be done with caution. Patients should be adequately hydrated and the need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

Co-administration of NSAIDs and ciclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus because of NSAID effects on renal prostaglandins. Renal function should be monitored when PERICOB 40 and any of these medicines are co-administered.

PERICOB 40 may be co-administered with opioid analgesics. The daily requirement for PRN opioids is significantly reduced when co-administered with parecoxib.

Effects of other medicines on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. It was demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62 % and 19 %, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of PERICOB 40 should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38 % and 24 %, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicines

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering PERICOB 40 and medicines that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46 % following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected.

These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering PERICOB 40 with medicines known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In two pharmacokinetic interaction studies in rheumatoid arthritis patients receiving a stable weekly methotrexate dose (5 - 20 mg/week, as a single oral or intramuscular dose), orally administered valdecoxib (10 mg twice daily or 40 mg twice daily) had little or no effect on the steady-state plasma concentrations of methotrexate. However, caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate. Adequate monitoring of methotrexate-related toxicity should be considered when co-administering parecoxib and methotrexate.

Co-administration of valdecoxib and lithium produced significant decreases in lithium serum clearance (25 %) and renal clearance (30 %) with a 34 % higher serum exposure compared to lithium alone. Lithium serum concentration should be monitored closely when initiating or changing PERICOB 40 therapy in patients receiving lithium.

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

Injectable anaesthetics

Co-administration of IV parecoxib 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, co-administration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam.

Administration of IV parecoxib 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics

No formal interaction studies have been done. In surgery studies in which parecoxib was administered preoperatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib and the inhalation anaesthetic medicines nitrous oxide and isoflurane (see section 5.1).

4.6 Fertility, pregnancy and lactation

Use of PERICOB 40 is contraindicated in pregnancy and lactation (see section 4.3)

Pregnancy

Parecoxib is suspected to cause serious birth defects when administered during the last trimester of pregnancy because as with other medicines known to inhibit prostaglandin, it may cause premature closure of the ductus arteriosus or uterine inertia (see sections 4.3 and 5.1).

Regular use of non-steroidal inflammatory parecoxib may result in:

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to results in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals

given a prostaglandin synthesis inhibitor during the organogenetic period

Second and Third trimester.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.

Breastfeeding

PERICOB 40 must not be administered to women who breastfeed (see section 4.3). 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). PERICOB 40 must not be administered to women who breastfeed (see section 4.3).

Fertility

Because of its inhibitory effect on cyclooxygenase/prostaglandin synthesis, the use of PERICOB 40 is not recommended in women attempting to conceive (see sections 4.3 and 5.1).

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 PERICOB 40 should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reaction for PERICOB 40 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 PERICOB 40 have 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.

b. Tabulated summary of adverse reactions

Within each frequency grouping, adverse reactions are listed using MedDRA terminology and presented in order of decreasing seriousness.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Pharyngitis, alveolar osteitis (dry socket)

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Abnormal sternal serous wound drainage, wound infection
Blood and lymphatic system disorders	Frequent	Anaemia postoperative
	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Anaphylactoid reaction
Metabolism and nutrition disorders	Frequent	Hypokalaemia
	Less frequent	Hyperglycaemia, anorexia
Psychiatric disorders	Frequent	Agitation, insomnia
Nervous system disorders	Frequent	Hypoaesthesia, dizziness, somnolence
	Less frequent	Cerebrovascular disorder, cerebrovascular incidents (stroke)
Ear and labyrinth disorders	Less frequent	Ear pain, vertigo
Cardiac disorders	Frequent	Oedema peripheral
	Less frequent	Dysrhythmia, palpitations, cardiovascular thrombotic events, myocardial infarction, bradycardia, congestive heart failure, tachycardia
	Frequency unknown	Circulatory collapse
Vascular disorders	Frequent	Hypertension, hypotension

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Hypertension (aggravated), orthostatic hypotension, hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory insufficiency
	Less frequent	Pulmonary embolism
	Frequency unknown	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, vomiting, constipation, dyspepsia, flatulence
	Less frequent	Gastroduodenal ulceration, gastro-oesophageal reflux disease, dry mouth, abnormal gastrointestinal sounds
	Frequency unknown	Pancreatitis, oesophagitis, oedema mouth (perioral swelling)
Skin and subcutaneous tissue disorders	Frequent	Pruritus, hyperhidrosis
	Less frequent	Ecchymosis, rash, urticarial
	Frequency unknown	Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Frequent	Back pain
	Less frequent	Arthralgia

MedDRA system organ class	Frequency	Adverse reactions
Renal and urinary disorders	Frequent	Oliguria
	Less frequent	Renal failure acute
	Frequency unknown	Renal failure
General disorders and administration site conditions	Less frequent	Asthenia, injection site pain, injection site reaction
	Frequency unknown	Hypersensitivity reactions including anaphylaxis and angioedema
Investigations	Frequent	Increased blood creatinine
	Less frequent	Increased blood CPK, increased blood LDH, increased AST, increased ALT, increased BUN
Injury, poisoning and procedural complications	Less frequent	Post procedural complication (skin)

c. Description of selected adverse reactions

Toxic epidermal necrolysis has been reported in association with the use of valdecoxib and cannot be ruled out for parecoxib (see section 4.4). In addition, the following less frequent, serious adverse reactions have been reported in association with the use of NSAIDs and cannot be ruled out for PERICOB 40: 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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Reporting of overdose with parecoxib has been associated with adverse reactions which have also been described with recommended doses of parecoxib.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other Analgesics

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

Parecoxib sodium is an inactive prodrug for 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.

In animal models, the analgesic activity of valdecoxib is not reversible by naloxone.

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 at approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C following IV and IM administration.

Distribution

The volume of distribution of valdecoxib after its IV administration is approximately 55 litres (greater than total body water). 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.

Metabolism

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 GYP-independent glucuronidation of the sulfonamide 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 (CLJ 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 subjects

In healthy elderly subjects, the apparent oral clearance of valdecoxib 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. Because renal elimination of valdecoxib is not important to its disposition, 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

Disodium phosphate anhydrous

O-phosphoric acid (for pH adjustment), E338

Sodium hydroxide (for pH adjustment), E524

Water for injection

6.2 Incompatibilities

PERICOB 40 must not be mixed with other medicines except for those mentioned in section 6.6. PERICOB 40 and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (5 %) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and is therefore not recommended.

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

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

Injection into an IV line delivering glucose 50 mg/ml (5 %) in Ringer-Lactate solution for injection, or other IV fluids not listed in section 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

36 months

Chemical and physical in-use stability of the reconstituted solution, which should not be refrigerated or frozen, have been demonstrated for up to 24 hours at 25 °C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable medicines, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 12 hours at 25 °C.

6.4 Special precautions for storage

Store at or below 30 °C.

PERICOB 40 does not require any special storage conditions prior to reconstitution. For storage conditions of the reconstituted PERICOB 40 see section 6.3.

6.5 Nature and contents of container

PERICOB 40 powder for solution for injection: 5 ml Type I glass vial with bromobutyl rubber stopper and an aluminium flip off seal.

Pack size: 10 x 5 ml vials

6.6 Special precautions for disposal and other handling

For single use only. Any unused PERICOB 40 or waste material should be disposed of in accordance with local requirements.

Reconstitute PERICOB 40 with 2 ml sodium chloride solution (0,9 % w/v) using aseptic technique. The only other acceptable solvents for reconstitution are 5 % glucose intravenous infusion, 0,45 % sodium chloride and 5 % glucose injection. After reconstitution, PERICOB 40 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.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ascendis Pharma (Pty) Ltd

31 Georgian Crescent East

Bryanston

2191

8 REGISTRATION NUMBER

52/2.9/0995

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 June 2022

10 DATE OF REVISION OF THE TEXT