PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF MEDICINE

PERODYN 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.

Excipient with known effect

PERODYN 40 contains less than 1 mmol sodium (23 mg) per dose. When reconstituted in sodium chloride 9 mg/ml (0,9 %) solution, PERODYN 40 contains approximately 0,44 mmol of sodium per vial.

When reconstituted in sodium chloride 9 mg/ml (0,9 %) solution, the pH of reconstituted solution is within 7.5 to 8.5.

The osmolality of the reconstituted solution is 382 mOsm/kg when reconstituted in sodium chloride 9 mg/ml (0,9 %) solution.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White or almost white cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PERODYN 40 is indicated 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);
- 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

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

Safety and efficacy of PERODYN 40 injection 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 PERODYN 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 PERODYN 40. An optimal effect is achieved when PERODYN 40 is given at the end of hip replacement surgery, prior to opioid administration. In all clinical assessments PERODYN 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 PERODYN 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 PERODYN 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

Based on 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, PERODYN 40 should not be used (see section 4.3).

Paediatric populations

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

Method of administration

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 the medicinal product before administration, see section 6.6.

Precipitation may occur when PERODYN 40 is combined in a solution with other medicinal products and therefore PERODYN 40 must not be mixed with any other medicinal product, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after with a solution of known compatibility.

After reconstitution with acceptable solvents, PERODYN 40 may only be injected IV or IM, or into IV lines delivering the following:

- Sodium chloride 9 mg/ml (0,9 %) solution for injection/infusion;
- Glucose 50 mg/ml (5 %) solution for infusion;
- Sodium chloride 4,5 mg/ml (0,45 %) and glucose 50 mg/ml (5 %) solution for injection/infusion; or
- Ringer-Lactate solution for injection.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to parecoxib or to any of the excipients listed in section 6.1;
- History of previous serious allergic medicine reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome), toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulphonamides (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 allergic-type reactions after taking acetylsalicylic acid or NSAIDs or other cyclooxygenase-2 (COX-2) specific inhibitors;

- Severe impairment of hepatic function;
- Inflammatory bowel disease;
- Severe renal impairment;
- Post- and peri-operative analgesia in the setting of coronary artery bypass surgery (CABG);
- Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease;
- Congestive heart failure (NYHA II-IV);
- Pregnancy and lactation (see section 4.6);
- Children younger than 18 years.

4.4 Special warnings and precautions for use

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

Modes of administration

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

Cardiovascular effects

There appears to be a higher risk for cardiovascular events and thrombotic adverse events with higher doses and longer duration of treatment with PERODYN 40. The exact 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 studies in 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.

Caution is advised when PERODYN 40 is prescribed to patients with cardiovascular risk factors e.g., hypertension, diabetes, smoking and hypercholesterolaemia.

Acetylsalicylic acid and other NSAIDs

Because of its lack of platelet effects, PERODYN 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 PERODYN 40 with warfarin and other oral anticoagulants (see section 4.5). Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban) (see section 4.5). The concomitant use of PERODYN 40 with other non-acetylsalicylic acid NSAIDs should be avoided.

PERODYN 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 parecoxib, as contained in PERODYN 40. Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving PERODYN 40.

Concomitant use of PERODYN 40 with other anti-coagulant medicines may increase the risk of intra- and post-operative bleeding.

Because of the possibility for increased adverse reactions at higher doses of parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see section 4.2).

PERODYN 40 may cause to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. PERODYN 40 should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with PERODYN 40 and throughout the course of therapy. If blood pressure rises significantly, alternative treatment should be considered.

Gastrointestinal (GI) effects

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 PERODYN 40 is given concomitantly with acetylsalicylic acid (even at low doses).

Skin effects

Serious skin reactions which may be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, may occur when using PERODYN 40. PERODYN 40 should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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 physician.

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 (see section 4.8). Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering PERODYN 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.

PERODYN 40 should be used with caution in patients with severe renal impairment (creatinine clearance < 30 ml/min) or moderate hepatic impairment (Child-Pugh scale 7 – 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh

scale > 9) therefore PERODYN 40 is not recommended for use in these patients (see also sections 4.2 and 4.3). Caution should be used when initiating treatment with PERODYN 40 in patients with any form of dehydration. It is advisable to rehydrate patients first and then start therapy with PERODYN 40.

Fluid retention and oedema

Due to inhibition of prostaglandin synthesis, fluid retention and oedema may occur in patients receiving PERODYN 40; therefore, PERODYN 40 should not be used in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention those taking diuretic treatment or those otherwise at risk of hypovolemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored (see section 4.3). If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken.

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

Anaphylactoid reactions

Hypersensitivity reactions such as anaphylaxis and angioedema have been reported in post-marketing experience with valdecoxib and cannot be ruled out for parecoxib, as contained in PERODYN 40. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides. PERODYN 40 should be discontinued at the first sign of hypersensitivity.

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

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as PERODYN 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. Eosinophilia 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 PERODYN 40 and evaluate the patient immediately.

Risk of hypokalaemia and renal tubular acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of Non-steroidal Anti-inflammatory Agents (NSAIDs) at higher than recommended doses. This risk is increased with the use of codeine/NSAIDs as patients may become dependent on the codeine component. Presenting signs and symptoms included reduced level of consciousness and generalised weakness. NSAID-induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Children

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

4.5 Interaction with other medicines and other forms of interaction

General

In vitro studies with human hepatic microsomal systems showed no significant inhibitory effects on CYP3A4, 2D6, 2E1, and 1A2 isoforms by parecoxib or valdecoxib. Weak inhibitory activity was found for 2C9 and 2C19 isozymes. PERODYN 40 is rapidly hydrolysed to the active substance valdecoxib. In humans, studies demonstrated 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.

Aspirin

Parecoxib had no effect on aspirin-mediated inhibition of platelet aggregation or bleeding times in volunteers. Clinical trials indicate that parecoxib can be given with low dose aspirin (≤ 325 mg). Because of its lack of platelet effects, PERODYN 40 is not a substitute for aspirin for cardiovascular prophylaxis. There is no evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with PERODYN 40.

ACE-inhibitors

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

Ciclosporin or tacrolimus

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

Diuretics

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

Fluconazole and ketoconazole

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62 % and 19 %, respectively) when co-administered with fluconazole, indicating that the dose of PERODYN 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; however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

Lithium

PERODYN 40 may produce 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 PERODYN 40 therapy in patients receiving lithium.

Warfarin or similar medicines

Anticoagulant therapy should be monitored, particularly during the first few days after initiating PERODYN 40 therapy in patients receiving warfarin or similar medicines, since these patients have an increased risk of bleeding complications (see section 4.4).

Dextromethorphan and medicinal products that are predominantly metabolised by CYP2D6

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 parecoxib, as contained in PERODYN 40 and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g., flecainide, propafenone, metoprolol).

Glibenclamide

Co-administration of parecoxib, as contained in PERODYN 40 with glibenclamide (CYP3A4 substrate) did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

Substrates of CYP2C19

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 PERODYN 40 with medicinal products known to be substrates of CYP2C19 (e.g., phenytoin, diazepam, or imipramine).

Methotrexate

In rheumatoid arthritis patients receiving weekly methotrexate, PERODYN 40 do not have a clinically significant effect on the plasma exposure to methotrexate.

Injectable anaesthetics

Co-administration of PERODYN 40 with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) do not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics of IV propofol or IV midazolam. Additionally, co-administration with PERODYN 40 has no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Regular use of non-steroidal inflammatory drugs 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.

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

Fertility

The use of parecoxib inhibits cyclooxygenase/prostaglandin synthesis and 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 women.

4.7 Effects on ability to drive and use machines

Dizziness may occur during the use of PERODYN 40 and should be considered before patients drive or use machines.

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect

Infections and infestations	*Frequent*	Pharyngitis, alveolar osteitis (dry socket)
	Less frequent	Abnormal sternal serous wound drainage, wound infection
Blood and lymphatic system disorders	*Frequent*	Post-operative anaemia
	Less frequent	Thrombocytopenia
Immune system disorders	*Less frequent*	Anaphylactoid reaction, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Metabolism and nutrition disorders	*Frequent*	Hypokalaemia
	Less frequent	Hyperglycaemia, anorexia
Psychiatric disorders	*Frequent*	Agitation, insomnia
Nervous system disorders	*Frequent*	Hypoaesthesia, dizziness
	Less frequent	Cerebrovascular disorder, dry mouth
Ear and labyrinth disorders	*Less frequent*	Ear pain
Cardiac disorders	*Less frequent*	Bradycardia, peripheral oedema, aggravated hypertension, dysrhythmia, hypertension, palpitations, tachycardia, congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events
	Frequency unknown	Circulatory collapse

Neurological disorders	*Less frequent*	Cerebrovascular incidents (strokes)
Vascular disorders	*Frequent*	Hypotension; hypertension
	Less frequent	Hypertension (aggravated), orthostatic
Respiratory, thoracic and mediastinal disorders	*Frequent*	Respiratory insufficiency
	Less frequent	Pulmonary embolism
	Frequency unknown	Dyspnoea, bronchospasm
Gastrointestinal disorders	*Frequent*	Dyspepsia, flatulence, constipation, nausea, vomiting, abdominal pain
	Less frequent	Gastroduodenal ulceration, gastroesophageal reflux disease, dry mouth, gastrointestinal sounds abnormal, pancreatitis, oesophagitis, oedema mouth (perioral swelling)
Skin and subcutaneous tissue disorders	*Frequent*	Pruritus, increased sweating
	Less frequent	Ecchymosis, rash, skin post-operative complications, urticaria
	Frequency unknown	Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	*Frequent*	Back pain
	Less frequent	Arthralgia
Renal and urinary disorders	*Frequent*	Oliguria
	Less frequent	Acute renal failure

	Frequency unknown	Renal failure, renal tubular acidosis
General disorders and administration site conditions	*Frequent*	Oedema peripheral
	Less frequent	Asthenia, injection site pain, injection site reaction
	Frequency unknown	Hypersensitivity reactions including anaphylaxis and angioedema
Investigations	*Frequent*	Blood creatinine increased
	Less frequent	Increased AST, increased ALT increased blood urea, Blood CPK increased, blood LDH increased, SGOT increased, SGPT increased, BUN increased

b. Post-marketing surveillance

In post-marketing experience, the following serious adverse events may occur in association with the use of PERODYN 40:

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal failure, acute renal failure and hypersensitivity reactions including anaphylaxis and angioedema. Gastrointestinal disorders include nausea and vomiting. Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the NSAID component at higher than recommended doses due to dependence on the codeine component.

c. Paediatric populations

Use of PERODYN 40 is not recommended for children younger than 18 years.

d. 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

No symptoms of overdose have been observed with single IV doses of up to 200 mg of PERODYN 40 injection in healthy subjects. PERODYN 40 injection doses of 50 mg BID IV for 7 days did not result in any signs of toxicity.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other Analgesics

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_{max} following IV and IM administration.

Distribution

The volume of distribution of valdecoxib after its IV administration is approximately 55 L (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 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 ($t_{1/2}$) of valdecoxib is about 8 hours.

Elderly

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)

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

6.2 Incompatibilities

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

PERODYN 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 therefore is not recommended.

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

PERODYN 40 should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after 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.

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

6.3 Shelf life

Unopened vial

3 years.

After reconstitution

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 products, 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 the unopened vial at or below 25 °C in its original container. For storage conditions during reconstitution, see section 6.3.

6.5 Nature and contents of container

Type I clear colourless glass vials (5 ml) with a coated butyl rubber stopper, sealed with a blue flip-off cap on the aluminium overseal. PERODYN 40 is available in packs, each containing 1 vial, 5 vials or 10 vials.

6.6 Special precautions for disposal and other handling

PERODYN 40 must be reconstituted before use. PERODYN 40 is preservative free. Aseptic technique is required for its preparation.

Reconstitution solvents

Acceptable solvents for reconstitution of PERODYN 40 are:

- Sodium chloride 9 mg/ml (0,9 %) solution for injection/infusion;
- Glucose 50 mg/ml (5 %) solution for infusion;
- Sodium chloride 4,5 mg/ml (0,45 %) and glucose 50 mg/ml (5 %) solution for injection/infusion.

Reconstitution process

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib). Remove the blue flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, the liquid should be a clear solution. PERODYN 40 should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter is observed. PERODYN 40 should be administered within 24 hours of reconstitution (see section 6.3) or discarded.

The reconstituted product is isotonic.

IV-line solution compatibility

After reconstitution with acceptable solvents, PERODYN 40 may only be injected IV or IM, or into IV lines delivering:

- Sodium chloride 9 mg/ml (0,9 %) solution for injection/infusion;
- Glucose 50 mg/ml (5 %) solution for infusion;
- Sodium chloride 4,5 mg/ml (0,45 %) and glucose 50 mg/ml (5 %) solution for injection/infusion; or
- Ringer-Lactate solution for injection.

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

7 HOLDERS OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road

Midrand

South Africa

1686

8 REGISTRATION NUMBER(S)

52/2.9/0951

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

18 January 2022

10 DATE OF REVISION OF THE TEXT

08 June 2023