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.

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
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.

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.
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 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
March 2022

10 DATE OF REVISION OF THE TEXT
N.A.

TRINITY PHARMA

Tel: 010 594 5610. Email: PV@kahmagroup.co.za

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS S3

1 NAAM VAN DIE MEDISYNE
PERODYN 40 (Poeier vir Oplossing vir Inspuiting)

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke 5 ml flessie bevat 40 mg parekoksib (as 42,36 mg parekoksibnatrium). Na hersamestelling, is die konsentrasie parekoksib 20 mg/ml. Elke 2 ml gerekonstitueerde poeier bevat 40 mg of parekoksib.

Hulpstof met bekende effek
PERODYN 40 bevat minder as 1 mmol natrium (23 mg) per dosis. Wanneer dit hersaamgestel is in 9 mg/ml (0,9 %) natriumchloriedoplossing, bevat PERODYN 40 ongeveer 0,44 mmol natrium per flessie.

Wanneer dit hersaamgestel is in 9 mg / ml (0,9 %) natriumchloriedoplossing, is die pH van die gerekonstitueerde oplossing tussen 7,5 tot 8,5.

Die osmolaliteit van die gerekonstitueerde oplossing is 382 mOsm/kg wanneer dit in 9 mg/ml (0,9%) natriumchloriedoplossing hersaamgestel word.

Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1.

3 FARMASEUTIESE VORM
Poeier vir oplossing vir inspuiting.
Wit of naaswit koek of poeier.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
PERODYN 40 is geïndikeerd vir:
- Die korttermynbestuur van post-operatiewe pyn by pasiënte wat parenterale terapie benodig, en vir wanneer 'n soortgelyke voordeel nie uit orale terapie verkry kon word nie. (Daar word daaraan herinner dat pasiënte na alternatiewe orale terapie oorgeskakel moet word sodra dit klinies aangedui is);
- Die vermindering van post-operatiewe opioïed gebruik by pasiënte wat 'n heupvervangingsoperasie ondergaan het vir tot en met 48 uur.

4.2 Posologie en metode van toediening
Posologie
PERODYN 40 is slegs aangedui vir pasiënte met 'n behoefte aan parenterale terapie en vir wie 'n soortgelyke voordeel nie uit alternatiewe orale terapie verkry kon word nie. Dit word aanbeveel dat pasiënte oorgeskakel word na alternatiewe orale terapie sodra dit klinies aangedui is.

Aangesien die kardiovaskulêre risiko van PERODYN 40 kan toeneem met die dosis en die duur van die blootstelling, moet die kortste moontlike duur en die laagste effektiewe daaglikse dosis gebruik word. Die relevansie van hierdie bevindings vir die korttermyngebruik van PERODYN 40 in die post-operatiewe opset, is egter nie bestudeer nie.

Veiligheid en effektiwiteit van PERODYN 40 inspuiting is nie vasgestel vir gebruiksperiodes van meer as 96 uur nie.

Bestuur van post-operatiewe pyn
Die gewone aanbevole dosis is 'n enkele of aanvanklike 40 mg wat intraveneus (IV) of intramuskulêr (IM) toegedien word, gevolg elke 6 tot 12 uur deur 20 mg of 40 mg soos benodig, om nie 80 mg/dag te oorskry nie.

Indien dit gegee word by die aanbevole dosisse vir die akute pynbeheer, was die aanvang van analgesie 7 - 14 minute en het dit 'n piekeffek binne 2 uur bereik. Na 'n enkele dosis was die duur van die analgesie afhanklik van die dosis en kliniese pynmodel en het dit gewissel van 7 tot meer as 24 uur.

Gesamentlike gebruik met opioïed analgesie
Opioïed analgesie kan gelyktydig gebruik word met PERODYN 40 dosering soos beskryf in die paragraaf hierbo, vir post-operatiewe pynbeheer vir tot en met 48 uur. In 'n heupvervangingsoperasie-proef was die daaglikse vereistes vir 'n opioïed aansienlik verminder (20 – 40 %) wanneer dit saam met PERODYN 40 toegedien was. 'n Optimale effek word verkry wanneer PERODYN 40 aan die einde van die heupvervangingsoperasie gegee word, voor opioïed toediening. In alle kliniese assesserings was PERODYN 40 met 'n vaste tydsinterval toegedien (d.w.s., 12 uurliks), terwyl die opioïede toegedien was wanneer nodig (PRN-basis).

Spesiale populasies
Bejaardes
Dosisaanpassing by bejaardes is egter nie oor die algemeen nodig nie, alhoewel, vir ouer vroulike pasiënte wat minder as 50 kg weeg, moet behandeling geïnisieer word met die helfte van die gewone aanbevole dosis van PERODYN 40 en die maksimum daaglikse dosis tot 40 mg verminder word.

Hepatiese inkorting
Geen dosisaanpassing is oor die algemeen nodig by pasiënte met ligte hepatiese inkorting (Child-Pugh skaal 5 - 6) nie. Inisieer PERODYN 40 met omsigtigheid en teen die helfte van die gewone aanbevole dosis by pasiënte met matige hepatiese inkorting (Child-Pugh skaal 7 - 9) en verminder die maksimum daaglikse dosis tot 40 mg. Daar is geen kliniese ondervinding by pasiënte met ernstige hepatiese inkorting (Child-Pugh skaal > 9) nie; daarom word die gebruik daarvan nie aanbeveel by hierdie pasiënte nie (sien afdeling 4.3).

Renale inkorting
Op grond van farmakokinetika is geen dosisaanpassing nodig by pasiënte met ligte tot matige (kreatinienopruiming van 30 - 80 ml/min) renale inkorting nie. By pasiënte met ernstige (kreatinienopruiming < 30 ml/min) renale inkorting of pasiënte wat geneig is tot vloeistofretensie, moet PERODYN 40 nie gebruik word nie (sien afdeling 4.3).

Pediatriese populasie
PERODYN 40 is nie bestudeer by pasiënte jonger as 18 jaar nie. Dus, word die gebruik daarvan nie by hierdie pasiënte aanbeveel nie.

Metode van toediening
Die IV bolus-inspuiting kan vinnig en direk in 'n aar of in 'n bestaande IV-lyn gegee word. Die IM-inspuiting moet stadig en diep in die spier gegee word. Vir instruksies oor die hersamestelling van die medisinale produk voor toediening, sien afdeling 6.6.

Presipitasie kan voorkom wanneer PERODYN 40 in 'n oplossing met ander medisyne gekombineer word, en daarom moet PERODYN 40 nie met enige ander medisyne gemeng word nie, hetsy tydens hersamestelling of inspuiting. In daardie pasiënte waar dieselfde IV-lyn gebruik moet word om 'n ander medisinale produk in te spuit, moet die lyn voldoende gespoel word voor en na die tyd met 'n oplossing van bekende verenigbaarheid.

Na hersamestelling met aanvaarbare oplosmiddels, mag PERODYN 40 slegs IV of IM ingespuit word, of in IV-lyne met die volgende:
- Natriumchloried 9 mg/ml (0,9 %) oplossing vir inspuiting/infusie;
- Glukose 50 mg/ml (5 %) oplossing vir infusie;
- Natriumchloried 4,5 mg/ml (0,45 %) en glukose 50 mg/ml (5 %) oplossing vir inspuiting/infusie; of
- Ringer-Laktaatoplossing vir inspuiting.

Inspuiting in 'n IV-lyn van 50 mg/ml (5 %) glukose in Ringer-Laktaatoplossing vir inspuiting of ander IV-vloeistowwe wat nie hierbo gelys is nie, word nie aanbeveel nie, aangesien dit presipitasie van die oplossing kan veroorsaak.

Vir instruksies oor die hersamestelling van die medisinale produk voor toediening, sien afdeling 6.6.

4.3 Kontraïndikasies
- Hipersensitiwiteit vir parekoksib of vir enige van die hulpstowwe gelys in afdeling 6.1;
- Geskiedenis van vorige ernstige allergiese medisyne-reaksies van enige aard, veral kutane reaksies soos Stevens-Johnson-sindroom, medisyne-reaksie met eosinofilie en sistemiese simptoom sindroom (MRESS-sindroom), toksiese epidermale nekrolise, eriteem multiforme of pasiënte met 'n bekende hipersensitiwiteit vir sulfonamiede (sien afdelings 4.4 en 4.8);
- Aktiewe peptiese ulserasie of gastro-intestinale (GI) bloeding;
- Pasiënte wat brongospasma, akute rinitis, nasale poliepe, angioedeem, urtikarie of allergiese-tipe reaksies ervaar het na die inname van asetielsalisielsuur of NSAIMs of ander siklooksigenase-2 (SOK-2) spesifieke inhibeerders;
- Erge inperking van hepatiese funksie;
- Inflammatoriese dermsiekte;
- Erge renale inkorting;
- Post- en peri-operatiewe analgesie teen die agtergrond van koronêre arterie omleidingschirurgie (CABG);
- Gevestigde iskemiese hartsiektes en/of serebrovaskulêre siektes (beroerte) en perifere arteriële siekte
- Kongestiewe hartversaking (NYHA II-IV);
- Swangerskap en laktasie (sien afdeling 4.6);
- Kinders jonger as 18 jaar.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
PERODYN 40 mag predisponeer tot kardiovaskulêre insidente, serebrovaskulêre insidente, gastroïntestinale insidente of kutane reaksies, wat noodlottig kan wees.

Metodes van toediening
Metodes van toediening anders as IV of IM (bv., intra-artikulêr, intratekale) is nie bestudeer nie en moet nie gebruik word nie.

Kardiovaskulêre effekte
Dit wil voorkom asof daar 'n hoër risiko is vir kardiovaskulêre insidente en trombotiese newe-effekte met hoër dosisse en langer duur van die behandeling met PERODYN 40. Die presiese omvang van die risiko verbonde aan 'n enkele dosis is nie bepaal nie, en die presiese duur van die terapie word nie met verhoogde risiko geassosieer nie.

Twee afsonderlike studies in koronêre arterie omleidingschirurgie (CABG) het getoon dat pasiënte wat parekoksib ontvang het vir 'n minimum van 3 dae, gevolg deur valdekoksib (die aktiewe metaboliet van parekoksib) vir 7 - 14 dae, het 'n verhoogde voorkoms van kardiovaskulêre/trombo-emboliese insidente gehad (bv., miokardiale infarksie en serebrovaskulêre ongeluk) in vergelyking met diegene wat placebo ontvang het.

Sorg word aanbeveel wanneer PERODYN 40 voorgeskryf word aan pasiënte met kardiovaskulêre risikofaktore, bv., hipertensie, diabetes, rook en hipercholesterolemie.

Asetielsalisielsuur en ander NSAIMs
Vanweë die gebrek aan plaatjie-effekte, is PERODYN 40 nie 'n plaasvervanger vir aspirien vir kardiovaskulêre profilakse nie. Daarom moet anti-plaatjie terapie nie gestaak word nie (sien afdeling 5.1). Sorg word aanbeveel wanneer PERODYN 40 saam met warfarien en ander orale antikoagulante toegedien word (sien afdeling 4.5). Orale antikoagulante sluit in warfarien/kumarien-tipe en nuwe orale antikoagulante (bv., apiksabaan, dabigatran en rivaroksabaan) (sien afdeling 4.5). Die gesamentlike gebruik van PERODYN 40 met ander nie-asetielsalisielsuur NSAIMs moet vermy word.

PERODYN 40 kan koors en ander tekens van inflammasie masker (sien afdeling 5.1). In geïsoleerde gevalle is 'n verergering van sagteweefselinfeksies aangemeld in verband met die gebruik van NSAIMs en in nie-kliniese studies met parekoksib, soos bevat in PERODYN 40. Sorg word aanbeveel by die monitering van die insisie vir tekens van infeksie by chirurgiese pasiënte wat PERODYN 40 ontvang.

Gelyktydige gebruik van PERODYN 40 met ander antikoagulant-medisyne kan die risiko van intra- en post-operatiewe bloeding verhoog.

Vanweë die moontlikheid van verhoogde newe-effekte by hoër dosisse parekoksib, ander SOK-2 inhibeerders en NSAIMs, moet pasiënte wat met parekoksib behandel word nagesien word met dosisverhoging en, in die afwesigheid van 'n toename in effektiwiteit, moet ander terapeutiese opsies oorweeg word (sien afdeling 4.2).

PERODYN 40 mag lei tot die aanvang van nuwe hipertensie of verergering van voorafbestaande hipertensie, wat albei kan bydra tot die verhoogde voorkoms van kardiovaskulêre insidente. PERODYN 40 moet met omsigtigheid gebruik word by pasiënte met hipertensie. Bloeddruk moet noukeurig gemonitor word tydens die aanvang van die behandeling met PERODYN 40 en gedurende die verloop van die behandeling. Indien die bloeddruk aansienlik styg, moet alternatiewe behandeling oorweeg word.

Gastroïntestinale (GI) effekte
Boonste gastroïntestinale (GI) komplikasies (perforasies, ulkusse of bloeding [PUBs]), waarvan sommige 'n noodlottig uitkoms gehad het, het voorgekom by pasiënte wat met parekoksib behandel was. Sorg word aanbeveel met die behandeling van pasiënte met die grootste risiko om gastroïntestinale komplikasies met NSAIMs te ontwikkel; bejaardes of pasiënte met 'n vorige geskiedenis van gastroïntestinale siekte, soos ulserasie en GI bloeding of pasiënte wat gelyktydig asetielsalisielsuur gebruik. Die NSAIM-klas word ook geassosieer met verhoogde GI-komplikasies wanneer dit gesamentlik toegedien word met glukokortikoïede, selektiewe serotonien heropname-remmers, ander anti-plaatjie medisyne, ander NSAIMs of pasiënte wat alkohol inneem. Daar is 'n verdere toename in die risiko van gastro-intestinale newe-effekte (gastroïntestinale ulserasie of ander gastroïntestinale komplikasies) wanneer PERODYN 40 gelyktydig met asetielsalisielsuur (selfs in lae dosisse) gegee word.

Vel effekte
Ernstige velreaksies wat fataal kan wees, insluitend eksfoliatiewe dermatitis, Stevens-Johnson sindroom en toksiese epidermale nekrolise, kan voorkom wanneer PERODYN 40 gebruik word. PERODYN 40 moet gestaak word met die eerste voorkoms van veluitslag of enige ander teken van hipersensitiwiteit.

Toepaslike maatreëls moet geneem word deur mediese praktisyns om te monitor vir ernstige velreaksies met behandeling, bv. addisionele pasiëntkonsultasies. Pasiënte moet geadviseer word om onmiddellik enige veltoestand wat te voorskyn kom by hul dokter aan te meld.

Dit is bekend dat ernstige velreaksies voorkom met NSAIMs, insluitend selektiewe SOK-2 inhibeerders, sowel as ander medisinale produkte. Die gerapporteerde tempo van ernstige velreaksies blyk egter groter te wees vir valdekoksib (die aktiewe metaboliet van parekoksib) in vergelyking met ander selektiewe SOK-2 inhibeerders. Pasiënte met 'n geskiedenis van sulfonamiedallergie kan 'n groter risiko vir velreaksies hê (sien afdeling 4.3). Pasiënte sonder 'n geskiedenis van sulfonamiedallergie kan ook moontlik op risiko wees vir ernstige velreaksies.

Renale en hepatiese effekte
Akute nierversaking is gerapporteer deur na-bemarking waarneming by pasiënte wat parekoksib ontvang (sien afdeling 4.8). Aangesien prostaglandiensintese-inhibisie kan lei tot die verswakking van die renale funksie en vloeistofretensie, moet omsigtigheid toegepas word met die toediening van PERODYN 40 by pasiënte met verswakte renale funksie (sien afdeling 4.2) of hipertensie, of by pasiënte met 'n gekompromitteerde hart- of hepatiese funksie of ander toestande wat geneig is tot vloeistofretensie.

PERODYN 40 moet met omsigtigheid gebruik word by pasiënte met ernstige renale inkorting (kreatinienopruiming < 30 ml/min) of matige hepatiese inkorting (Child-Pugh skaal 7 - 9). Daar is geen kliniese ondervinding by pasiënte met ernstige hepatiese inkorting (Child-Pugh skaal > 9) nie, daarom word PERODYN 40 nie aanbeveel vir gebruik by hierdie pasiënte nie (sien ook afdelings 4.2 en 4.3). Sorg word aanbeveel met die inisiëring van behandeling met PERODYN 40 by pasiënte met enige vorm van dehidrasie. Dit is raadsaam om pasiënte eers te hidreer en dan behandeling met PERODYN 40 te begin.

Vloeistofretensie en edeem
Vanweë die inhibisie van prostaglandiensintese, kan vloeistofretensie en edeem voorkom by pasiënte wat PERODYN 40 ontvang; dus, moet PERODYN 40 nie gebruik word by pasiënte met 'n gekompromitteerde kardiale funksie en ander toestande wat predisponeer na, óf vererger kan word, deur vloeistof retensie, diegene wat diuretiese behandeling neem, of diegene wat andersins op risiko is vir hipovolemie. Pasiënte met bestaande kongestiewe hartversaking of hipertensie moet noukeurig gemonitor word (sien afdeling 4.3). Indien daar kliniese bewyse is van die verswakking in die toestand van hierdie pasiënte, moet toepaslike maatreëls, insluitend die staking van parekoksib, geneem word.

Sorg moet toegepas word met die inisiëring van behandeling met PERODYN 40 by pasiënte met dehidrasie. In hierdie geval is dit raadsaam om pasiënte eers te hidreer en dan behandeling met PERODYN 40 te begin.

Anafilakotoïede reaksies
Hipersensitiwiteitsreaksies soos anafilakse en angioedeem is aangemeld in na-bemarking waarneming met valdekoksib, en dit kan nie uitgesluit word vir parekoksib, soos bevat in PERODYN 40, nie. Sommige van hierdie reaksies het voorgekom by pasiënte met 'n geskiedenis van allergiese-tipe reaksies op sulfonamiede. PERODYN 40 moet gestaak word met die eerste teken van hipersensitiwiteit.

Gevalle van erge hipotensie kort na toediening van parekoksib is in na-bemarking waarneming aangemeld. Sommige van hierdie gevalle het voorgekom sonder ander tekens van anafilakse. Die geneesheer moet voorbereid wees om erge hipotensie te behandel.

Risiko vir Medisyne Reaksie met Eosinofilie en Sistemiese Simptome (MRESS)
Medisyne Reaksie met Eosinofilie en Sistemiese Simptome (MRESS) is aangemeld by pasiënte wat NSAIMs neem, soos PERODYN 40. Sommige van hierdie insidente was fataal of lewensgevaarlik. MRESS oor die algemeen, hoewel nie uitsluitlik nie, presenteer met koors, uitslag, limfadenopatie en/of gesigswelling. Ander kliniese manifestasies kan hepatitis, nefritis, hematologiese abnormaliteite, miokarditis of miositis insluit. Soms kan simptome van MRESS lyk soos 'n akute virusinfeksie. Eosinofilie is gereeld teenwoordig. Omdat hierdie afwyking wisselvallig is in aanbieding, kan ander orgaanstelsels wat nie hier genoem word nie, betrokke wees. Dit is belangrik om daarop te let dat vroeë manifestasies van hipersensitiwiteit, soos koors of limfadenopatie, kan voorkom, selfs al is daar nie 'n uitslag nie. As sulke tekens of simptome voorkom, staak PERODYN 40 en evalueer die pasiënt onmiddellik.

Kinders
PERODYN 40 is nie bestudeer by pasiënte jonger as 18 jaar nie. Dus, word die gebruik daarvan nie by hierdie pasiënte aanbeveel nie.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Algemeen
In vitro studies met menslike hepatiese mikrosomale stelsels het geen noemenswaardige inhiberende effekte op CYP3A4, 2D6, 2E1 en 1A2 isovorme deur parekoksib of valdekoksib getoon nie. Swak inhiberende aktiwiteit is gevind vir 2C9 en 2C19 isosieme. PERODYN 40 word vinnig gehidroliseer tot die aktiewe stof valdekoksib. By mense het studies getoon dat valdekoksib metabolisme hoofsaaklik bemiddel word via sitochroom P450 CYP3A4 en 2C9 isosieme. Glukuronidasie is 'n verdere roete van metabolisme. Die alternatiewe CYP-gemedieerde en nie-CYP-gemedieerde metaboliese weë kan die waarskynlikheid verminder dat individue met genetiese polimorfismes aansienlik hoër plasmakonsentrasies het as gevolg van verswakte metabolisme.

Aspirien
Parekoksib het geen effek op aspirien-gemedieerde inhibisie van plaatjie-aggregasie of bloedingstye by vrywilligers gehad nie. Kliniese proewe dui aan dat parekoksib gegee kan word met 'n lae dosis aspirien (≤ 325 mg). Vanweë die gebrek aan plaatjie-effekte, is PERODYN 40 nie 'n plaasvervanger vir aspirien vir kardiovaskulêre profilakse nie. Daar is geen bewyse dat gelyktydige gebruik van aspirien die verhoogde risiko vir ernstige kardiovaskulêre trombotiese insidente wat verband hou met PERODYN 40 verminder nie.

AOE-inhibeerders
Inhibisie van PERODYN 40 kan die anti-hipertensiewe effek van angiotensienomskakelende ensiem (AOE)-inhibeerders verminder. Hierdie interaksie moet in ag geneem word by pasiënte wat PERODYN 40 ontvang, tesame met AOE-inhibeerders.

Siklosporien of takrolimus
Gesamentlike toediening van PERODYN 40 en siklosporien of takrolimus kan die nefrotoksiese effek van siklosporien en takrolimus verhoog. Renale funksie moet gemonitor word wanneer PERODYN 40 en enige van hierdie medisyne saam toegedien word.

Diuretika
PERODYN 40 kan die natriuretiese effek van furosemied en tiasiede verminder deur die inhibisie van renale prostaglandiensintese.

Flukonasool en ketokonasool
Plasma-blootstelling (AOK en K_{maks}) aan valdekoksib is verhoog (onderskeidelik 62 % en 19 %) wanneer dit saam met flukonasool toegedien word, wat daarop dui dat die dosis PERODYN 40 verminder moet word by pasiënte wat flukonasool-terapie ontvang. Plasma-blootstelling (AOK en K_{maks}) aan valdekoksib is verhoog (onderskeidelik 38 % en 24 %) wanneer dit saam met ketokonasool toegedien word; 'n dosisaanpassing is egter meestal nie nodig vir pasiënte wat ketokonasool ontvang nie.

Litium
PERODYN 40 kan aansienlike afname in litiumserumopruiming (25 %) en renale opruiming (30 %) veroorsaak met 'n 34 % hoër blootstelling aan serum in vergelyking met litium alleen. Litiumserumkonsentrasie moet noukeurig gemonitor word wanneer PERODYN 40-terapie geïnisieer of verander word by pasiënte wat litium ontvang.

Warfarien of soortgelyke medisyne
Antikoagulanteterapie moet gemonitor word, veral gedurende die eerste paar dae na die inisiasie van PERODYN 40 terapie by pasiënte wat warfarien of soortgelyke medisyne ontvang, aangesien hierdie pasiënte 'n groter risiko vir bloedings komplikasies het (sien afdeling 4.4).

Dekstrometorfaan en medisinale produkte wat hoofsaaklik deur CYP2D6 gemetaboliseer word
Behandeling met valdekoksib (40 mg twee maal per dag vir 7 dae) het 'n 3-voudige toename in plasmakonsentrasies van dekstrometorfaan (CYP2D6-substraat) veroorsaak. Dus, moet sorg uitgeoefen word met die gesamentlike toediening van parekoksib, soos bevat in PERODYN 40 en medisinale produkte wat hoofsaaklik deur CYP2D6 gemetaboliseer word en wat noue terapeutiese grense het (bv., flekainied, propafenoon, metoprolol).

Glibenklamied
Gesamentlike toediening van parekoksib, soos bevat in PERODYN 40 met glibenklamied (CYP3A4 substraat), het nie die farmakokinetika (blootstelling) of die farmakodinamika (bloedglukose en insulienvlakke) van glibenklamied beïnvloed nie.

Substrate van CYP2C19
Plasma blootstelling van omeprasool (CYP2C19 substraat) 40 mg een maal per dag was met 46 % verhoog na toediening van valdekoksib 40 mg twee maal per dag vir 7 dae, terwyl die plasma blootstelling aan valdekoksib nie beïnvloed was nie. Hierdie resultate dui daarop dat, hoewel valdekoksib nie deur CYP2C19 gemetaboliseer word nie, dit 'n inhibeerder van hierdie iso-ensiem kan wees. Dus, moet sorg toegepas word wanneer PERODYN 40 toegedien word met medisinale produkte wat bekend is om substrate van CYP2C19 te wees (bv., fenitoïen, diasepaam of imipramien).

Metotreksaat
By rumatoïede artritis pasiënte wat weekliks metotreksaat ontvang, het PERODYN 40 geen klinies beduidende effek op die plasma-blootstelling aan metotreksaat gehad nie.

Inspuitbare anestetika
Gesamentlike toediening van PERODYN 40 met propofol (CYP2C9 substraat) of midasolam (CYP3A4-substraat) het nie die farmakokinetika (metabolisme en blootstelling) of die farmakodinamika van IV propofol of IV midasolam beïnvloed nie. Daarbenewens het die gesamentlike toediening van PERODYN 40 geen noemenswaardige effek op die farmakokinetika van IV fentaniel óf IV alfentaniel (CYP3A4-substraat) nie.

Inhalasie anestetika
In 'n post-ortopediese studie was parenterale parekoksib pre-operatief toegedien en geen bewyse van medisyne-interaksie was waargeneem by pasiënte wat parenterale parekoksib en die inhalasie anestetiese middels, stikstofoksied en isofluraan ontvang het nie.

4.6 Vrugbaarheid, swangerskap en laktasie
Die gebruik van PERODYN 40 is gekontraïndikeerd tydens swangerskap en laktasie (sien afdeling 4.3).

Swangerskap
Gereelde gebruik van nie-steroïdale inflammatoriese middels kan lei tot:
Eerste trimester
Inhibisie van prostaglandien sintese kan swangerskap en/of die embrio/fetus ontwikkeling nadelig beïnvloed. Data vanuit epidemiologiese studies wek kommer oor 'n verhoogde risiko van miskraam en kardiale afwyking en gastroskise na die gebruik van 'n prostaglandien sintese inhibeerder in die vroeë swangerskap. Die absolute risiko vir kardiovaskulêre misvorming het toegeneem van minder as 1 % tot ongeveer 1,5 %. In diere, is getoon dat toediening van 'n prostaglandien sintese inhibeerder verhoogde voor- en na-inplantingsverlies en embrio-fetale sterftes tot gevolg het. Daarbenewens is verhoogde voorvalle van verskillende misvormings, insluitend kardiovaskulêre, gerapporteer by diere wat gedurende die organogenetiese periode 'n prostaglandien sintese inhibeerder gekry het.
Twede en derde trimester
Gedurende die derde trimester van swangerskap kan prostaglandien sintese inhibeerders die fetus blootstel aan: kardiopulmonêre toksisiteit (met premature sluiting van die ductus arteriosus en pulmonale hipertensie); renale disfunksie, wat kan lei tot nierversaking met oligo-hidroamniose. Aan die einde van die swangerskap kan die moeder en die neonaat moontlik blootgestel word aan moontlike verlenging van bloedingstyd, 'n teenaggregerende effek wat selfs by baie lae dosisse kan voorkom; inhibering van uteriene kontraksies wat lei tot vertraagde of verlengde parturisie.

Borsvoeding
Toediening van 'n enkele dosis parekoksib aan lakterende vroue na keisersnee het gelei tot die oordrag van 'n relatiewe klein hoeveelheid parekoksib en die aktiewe metaboliet valdekoksib in menslike melk, en dit het gelei tot 'n lae relatiewe dosis vir die baba. PERODYN 40 moet nie toegedien word aan vroue wat borsvoed nie (sien afdeling 4.3).

Vrugbaarheid
Die gebruik van parekoksib inhibeer siklo-oksigenase/prostaglandiensintese en word nie aanbeveel by vroue wat probeer swanger word nie. Op grond van die werkingsmeganisme, kan die gebruik van NSAIDs die skeuring van die ovariale follikels vertraag of verhoed, wat geassosieer word met omkeerbare onvrugbaarheid by vroue.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik
Duiseligheid kan voorkom tydens die gebruik van PERODYN 40 en moet oorweeg word voordat pasiënte bestuur of masjiene gebruik.

4.8 Newe-effekte
a. **Getabuleerde opsomming van newe-effekte**
Sisteem-orgaanklas
Frekwensie
Nadelige effekte
Infeksies en infestasies
Gereeld
Faringitis, alveolêre osteïtis (alveolalgie)

Minder gereeld
Abnormale sternale erge wond dreinering, wondinfeksie
Bloed- en Limfatiese Sisteemversteurings
Gereeld
Post-operatiewe anemie

Minder gereeld
Trombositopenie
Immuunstelselversteurings
Minder gereeld
Anafilakotoïede reaksie, Medisyne Reaksie met Eosinofilie en Sistemiese Simptome (MRESS) (sien afdeling 4.4)
Metabolisme- en voedingsversteurings
Gereeld
Hipokalemie

Minder gereeld
Hiperglisemie, anoreksie
Psigiatriese versteurings
Gereeld
Agitasie, insomnie
Senusisteemversteurings
Gereeld
Hipo-estesie, duiseligheid

Minder gereeld
Serebrovaskulêre afwyking, droë mond
Oor- en doolhofversteurings
Minder gereeld
Oorpyn
Kardiale versteurings
Minder gereeld
Bradikardie, perifere edeem, verergerde hipertensie, disritmie, hipertensie, palpitasies, tagikardie, kongestiewe hartversaking, miokardiale infarksie, kardiovaskulêre trombotiese insidente

Frekwensie onbekend
Sirkulatoriese ineenstorting

Neurologiese versteurings
Minder gereeld
Serebrovaskulêre insidente (beroertes)
Vaskulêre versteurings
Gereeld
Hipotensie; hipertensie

Minder gereeld
Hipertensie (verergerd), ortostaties
Respiratories-, torakale- en mediastinale versteurings
Gereeld
Respiratoriese ontoereikendheid

Minder gereeld
Pulmonêre embolisme

Frekwensie onbekend
Dispnee, brongospasma
Gastroïntestinale versteurings
Gereeld
Dispepsie, winderigheid, konstipasie, naarheid, braking, abdominale pyn

Minder gereeld
Gastro-duodenale ulserasie, gastroesofageale reflukssiekte, droë mond, abnormale gastroïntestinale geluide, pankreatitis, esofagitis, mond edeem (peri-orale swelling)
Vel- en Onderhuidse weefselversteurings
Gereeld
Pruritus, verhoogde sweet

Minder gereeld
Eggimose, uitslag, post-operatiewe vel komplikasies, urtikarie

Frekwensie onbekend
Stevens-Johnson sindroom, eriteem multiforme, eksfoliatiewe dermatitis, toksiese epidermale nekrolise
Muskuloskeletale bindweefselversteurings
Gereeld
Rugpyn

Minder gereeld
Artralgie
Nier- en urienweg afwykings
Gereeld
Oligurie

Minder gereeld
Akute renale versaking

Frekwensie onbekend
Renale versaking
Algemene siektes en toedieningsarea toestande
Gereeld
Perifere edeem

Minder gereeld
Astenie, pyn op die inspuitplek, reaksie op die inspuitplek

Frekwensie onbekend
Hipersensitiwiteit reaksies insluitend anafilakse en angioedeem
Ondersoeke
Gereeld
Verhoogde bloed kreatien

Minder gereeld
Verhoogde AST, verhoogde ALT, verhoogde bloed ureum, verhoogde bloed KFK, verhoogde bloed LDH, verhoogde SGOT, verhoogde SGPT, verhoogde BUN

b. **Na-bemarkingservaring**
In na-bemarkingservaring, kan die volgende ernstige nadelige effekte voorkom in assosiasie met die gebruik van PERODYN 40:
Eriteem multiforme, Stevens-Johnson sindroom, toksiese epidermale nekrolise, renale versaking, akute renale versaking en hipersensitiwiteitsreaksies, insluitend anafilakse en angioedeem. Gastroïntestinale afwykings sluit in naarheid en braking.

c. **Pediatriese populasies**
Die gebruik van PERODYN 40 word nie aanbeveel vir kinders jonger as 18 jaar nie.

d. **Rapportering van vermoedelike newe-effekte**
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "**6.04 Adverse Drug Reactions Reporting Form**", wat aanlyn by SAHPRA se publikasies gevind kan word:
https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
Geen simptome van oordosering was waargeneem met enkele IV doserings van soveel as 200 mg PERODYN 40 inspuiting by gesonde persone nie. PERODYN 40 inspuitingsdosisse van 50 mg BID IV vir 7 dae het geen tekens van toksisiteit tot gevolg gehad nie.
In geval van oordosering, moet pasiënte bestuur word met simptomatiese en ondersteunende sorg.

5 FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
A 2.9 Ander Analgetika

Parekoksibnatrium is 'n onaktiewe progeneesmiddel vir valdekoksib. Na inspuiting word parekoksib vinnig gehidroliseer na valdekoksib, wat aktief is in dieremodelle van prostaglandien-afhanklike pyn, inflammasie en koors. Die werkingsmeganisme van valdekoksib is hoofsaaklik deur die inhibisie van SOK-2-gemedieerde prostaglandiensintese. By terapeutiese dosisse is valdekoksib 'n spesifieke SOK-2 inhibeerder en inhibeer dit nie SOK-1 nie. In dieremodelle is die pynstillende aktiwiteit van valdekoksib nie omkeerbaar deur naloksoon nie.

5.2 Farmakokinetiese eienskappe
Na IV of IM inspuiting word parekoksib vinnig omgeskakel na valdekoksib, die farmakologiese komponent, deur ensiematiese hidrolise in die lewer.

Absorpsie
Blootstelling van valdekoksib na enkele dosisse parekoksib inspuiting, gemeet aan beide die area onder die plasmakonsentrasie teenoor tydkurwe (AOK) en piek konsentrasie (K_{maks}) is ongeveer lineêr in die kliniese dosisreeks. AOK en K_{maks} na twee maal per dag (BID) toediening van valdekoksib is lineêr tot 50 mg IV en 20 mg IM. Die gelykvlak plasmakonsentrasies van valdekoksib word binne vier dae met BID-dosering bereik. Na enkele IV en IM dosisse van parekoksibnatrium 20 mg, word K_{maks} van valdekoksib onderskeidelik ongeveer 30 minute en ongeveer 1 uur bereik. Blootstelling aan valdekoksib is soortgelyk in terme van AOK en K_{maks} na IV en IM toediening.

Verspreiding
Die volume van distribusie van valdekoksib na die IV toediening is ongeveer 55 L (groter as totale liggaamswater). Plasmaproteïenbinding is ongeveer 98 % oor die konsentrasie reikwydte wat bereik word met die hoogste aanbevole dosis, 80 mg/dag. Valdekoksib, maar nie parekoksib nie, word breedvoerig in eritrosiete verdeel.

Metabolisme
Parekoksib word vinnig en byna volledig omgeskakel na valdekoksib *in vivo* met 'n plasma-halfleeftyd van ongeveer 22 minute. Die eliminasie van valdekoksib is deur ekstensiewe hepatiese metabolisme wat veelvuldige weë insluit, insluitend sitochroom P450 CYP3A4 en CYP2C9 isoënsieme en CYP-onafhanklike glukuronidasie van die sulfonamiedgroep. 'n Gehidroksileerde metaboliet van valdekoksib (via die CYP-weg) is geïdentifiseer in menslike plasma wat aktief is as 'n SOK-2 inhibeerder. Dit verteenwoordig ongeveer 10 % van die konsentrasie van valdekoksib; maar as gevolg van die lae konsentrasie van hierdie metaboliet, word daar nie verwag dat dit 'n beduidende kliniese effek sal lewer na toediening van terapeutiese dosisse parekoksibnatrium nie. Die valdekoksib metaboliet ondergaan uitgebreide metabolisme, met minder as 5 % van die dosis wat in urine en feses uitgeskei word.

Eliminasie
Valdekoksib word uitgeskei deur middel van hepatiese metabolisme met minder as 5 % onveranderde medisyne wat in die urine teruggewin word. Geen onveranderde parekoksib word in urine opgespoor nie en slegs spoorhoeveelhede in die feses. Ongeveer 70 % van die dosis word in die urine as onaktiewe metaboliete uitgeskei. Plasmaopruiming (CLp) vir valdekoksib is ongeveer 6 L/uur. Na IV of IM dosering van parekoksibnatrium is die eliminasiehalfleeftyd ($t_{1/2}$) van valdekoksib ongeveer 8 uur.

Bejaardes
By gesonde bejaarde proefpersone, was die oënskynlike orale klaring van valdekoksib verlaag, wat gelei het tot 'n ongeveer 40 % hoër plasma-blootstelling van valdekoksib in vergelyking met gesonde jong proefpersone. Waar dit aangepas was vir liggaamsgewig, was die gelykvlak plasma blootstelling 16 % hoër by bejaarde vrouens in vergelyking met bejaarde mans.

Renale inkorting
By pasiënte met verskillende grade van renale inkorting, waar 20 mg IV parekoksib inspuiting as 'n enkele dosis toegedien was, was parekoksib vinnig uit die plasma opgeruim. Aangesien renale eliminasie van valdekoksib nie belangrik is vir die disposisie daarvan nie, was daar geen veranderinge in die opruiming van valdekoksib gevind nie, selfs nie by pasiënte met renale inkorting nie. Dosisse van meer as 20 mg was nie in renale inkorting bestudeer nie. Dus, op grond van farmakokinetika, is dosisaanpassing nie nodig by pasiënte met ligte tot matige renale inkorting nie.

Hepatiese inkorting
Matige hepatiese inkorting het nie gelei tot 'n daling in tempo óf omvang van parekoksib omskakeling na valdekoksib nie. By pasiënte met matige hepatiese inkorting (Child-Pugh skaal 7 - 9), moet die behandeling geïnisieer word met die helfte van die gewone aanbevole dosis parekoksib inspuiting en die maksimum daaglikse dosis moet verminder word tot 40 mg, aangesien valdekoksib blootstelling meer as verdubbel was (130 %) in hierdie pasiënte. Pasiënte met erge hepatiese inkorting was nie bestudeer nie en die gebruik van parekoksib inspuiting by pasiënte met erge hepatiese inkorting word dus nie aanbeveel nie.

6 FARMSEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Dinatriumfosfaat (anhedries)
Fosforsuur en/of natriumhidroksied (vir pH-aanpassing)

6.2 Onverenigbaarheid
PERODYN 40 mag nie met ander medisyne gemeng word nie, behalwe vir dié wat in afdeling 6.6 genoem word.

PERODYN 40 en opioïede moet nie saam toegedien word in dieselfde inspuiting nie.

Die gebruik van Ringer-Laktaatoplossing vir inspuiting of glukose 50 mg/ml (5 %) in Ringer-Laktaatoplossing vir inspuiting vir hersamestelling sal veroorsaak dat die parekoksib uit die oplossing presipiteer en daarom word dit nie aanbeveel nie.

Die gebruik van water vir inspuiting word nie aanbeveel nie, aangesien die resulterende oplossing nie isotonies is nie.

PERODYN 40 moet nie in 'n IV-lyn ingespuit word wat enige ander medisyne lewer nie. Die IV-lyn moet voldoende gespoel word voor en na die tyd met 'n oplossing van bekende verenigbaarheid (sien afdeling 6.6).

Om in 'n IV-lyn wat 50 mg/ml (5 %) glukose in Ringer-Laktaatoplossing vir inspuiting lewer óf ander IV-vloeistowwe wat nie in afdeling 6.6 gelys is nie, in te spuit word nie aanbeveel nie, aangesien dit presipitasie in die oplossing kan veroorsaak.

PERODYN 40 mag nie met ander medisyne gemeng word nie, behalwe dié wat in afdeling 6.6 genoem word.

6.3 Rakleeftyd
Onoopgemaakte flessie
3 jaar.

Na hersamestelling
Chemiese en fisiese stabiliteit tydens gebruik van die gerekonstitueerde oplossing, wat nie verkoel of gevries moet word nie, is gedemonstreer vir tot en met 24 uur by 25 °C. Dus, 24 uur moet beskou word as die maksimum rakleeftyd van die gerekonstitueerde produk. Alhoewel, vanweë die belangrikheid van mikrobiologiese infeksierisiko vir inspuitbare produkte, moet die gerekonstitueerde oplossing onmiddellik gebruik word, tensy hersamestelling plaasgevind het in gekontroleerde en gevalideerde aseptiese toestande. Tensy daar aan sulke vereistes voldoen word, is die in-bergings tye en toestande voor gebruik die verantwoordelikheid van die verbruiker en sal dit normaalweg nie langer as 12 uur by 25 °C wees nie.

6.4 Spesiale voorsorgmaatreëls tydens berging
Stoor die ongeopende flessie by of benede 25 °C in die oorspronklike houer. Vir bergingstoestande tydens hersamestelling, sien afdeling 6.3.

6.5 Aard en inhoud van die houer
Tipe I helder, kleurlose glasflessies (5 ml) met 'n bedekte butielrubberprop, verseël met 'n blou afwip-deksel op die aluminiumseël. PERODYN 40 is beskikbaar in pakke wat elk 10 flessies bevat.

6.6 Spesiale voorsorgmaatreëls vir wegdoen en ander hantering
PERODYN 40 moet hersaamgestel word voor gebruik. PERODYN 40 is vry van preserveermiddel. Aseptiese tegniek is nodig vir die voorbereiding daarvan.

Oplosmiddels
Aanvaarbare oplosmiddels vir PERODYN 40 is:
- Natriumchloried 9 mg/ml (0,9%) oplossing vir inspuiting/infusie;
- Glukose 50 mg/ml (5 %) oplossing vir infusie;
- Natriumchloried 4,5 mg / ml (0,45 %) en glukose 50 mg / ml (5 %) oplossing vir inspuiting/infusie.

Hersamestelling proses
Gebruik aseptiese tegnieke om gevriesdroogde parekoksib (as parekoksib) te rekonstrueer. Verwyder die blou afwip-deksel om die sentrale gedeelte van die rubberprop van die 40 mg parekoksib-flessie bloot te stel. Onttrek, met 'n steriele naald en spuit, 2 ml van 'n aanvaarbare oplosmiddel, plaas die naald deur die sentrale gedeelte van die rubberprop en plaas die oplosmiddel oor in die 40 mg-flessie. Los die poeier volledig op met behulp van 'n sagte draaibeweging en inspekteer die gerekonstitueerde produk voor gebruik. Die volledige inhoud van die flessie moet vir 'n enkele toediening onttrek word.

Na hersamestelling moet die vloeistof 'n helder oplossing wees. PERODYN 40 moet visueel geïnspekteer word vir deeltjies en verkleuring voor toediening. Die oplossing moet nie gebruik word as dit verkleur of troebel is, of as deeltjies sigbaar is nie. PERODYN 40 moet binne 24 uur na hersamestelling toegedien word (sien afdeling 6.3) of weggegooi word.

Die hersaamgestelde produk is isotonies.

IV-lyn oplossing verenigbaarheid
Na hersamestelling met aanvaarbare oplosmiddels, mag PERODYN 40 slegs IV of IM ingespuit word, of in IV-lyne met:
- Natriumchloried 9 mg/ml (0,9 %) oplossing vir inspuiting/infusie;
- Glukose 50 mg/ml (5 %) oplossing vir infusie;
- Natriumchloried 4,5 mg/ml (0,45 %) en glukose 50 mg/ml (5 %) oplossing vir inspuiting/infusie; of
- Ringer-Laktaatoplossing vir inspuiting.

Slegs vir eenmalige gebruik. Enige ongebruikte medisyne of afvalmateriaal moet weggedoen word volgens die plaaslike vereistes.

7 HOUER VAN REGISTRASIESERTIFIKAAT
Trinity Pharma (Pty) Ltd.
106 16th Weg
Midrand
Suid-Afrika
1686

8 REGISTRASIENOMMER(S)
52/2.9/0951

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
Maart 2022

10 DATE OF REVISION OF THE TEXT
N.A.