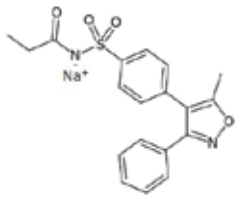
PRODUCT INFORMATION
PARECOXB parecoxib (as sodium)

NAME OF THE MEDICINE

PARECOXB parecoxib (as sodium) 40 mg powder for solution for injection.
The following structural formula of parecoxib sodium is shown below:



Chemical name: N-[[4-(5-methyl-3-phenyl-4 isoxazolyl) phenyl]sulfonyl] propanamide, sodium salt
Molecular formula: $C_{19}H_{17}N_2O_4SNa$
Molecular weight: 392.41
CAS number: 198470-85-8

DESCRIPTION

Parecoxib sodium is a white to off-white solid that is very soluble in water. The formulated drug product is soluble in normal (0.9%) saline at >50 mg/mL.
Powder for Injection and Powder and Diluent for Injection
PARECOXB Injection is a white to off-white, preservative-free, lyophilised powder in a single-use vial. For intravenous (IV) or intramuscular (IM) administration, PARECOXB Injection should be reconstituted with 2 mL sodium chloride solution (0.9% w/v), or a suitable alternative (see DOSAGE AND ADMINISTRATION).
Reconstituted Solution
The reconstituted solution is clear and colourless.
PARECOXB Injection 40 mg contains parecoxib sodium, sodium phosphate-dibasic anhydrous; phosphoric acid and/or sodium hydroxide may have been added to adjust pH.
When reconstituted in sodium chloride solution (0.9% w/v), PARECOXB Injection contains approximately 0.44 mEq of sodium per 40 mg vial.

PHARMACOLOGY

Pharmacological Actions

Pharmacodynamics

Following injection, parecoxib sodium is rapidly converted to valdecoxib: the *in vivo* pharmacology of parecoxib is therefore that of valdecoxib. The mechanism of action of valdecoxib is by inhibition of cyclooxygenase-2 (COX-2)-mediated prostaglandin synthesis. At therapeutic plasma concentrations in humans, valdecoxib does not inhibit cyclooxygenase-1 (COX-1). In animal models, valdecoxib is anti-inflammatory, analgesic, and antipyretic.
By inhibition of both peripheral and central COX-2, valdecoxib reduces the production of prostaglandins that are important mediators of pain and inflammation. Therefore, PARECOXB Injection is not expected to exhibit the potential for dependence, sedation or respiratory depression seen with opioid analgesic agents.

Pharmacokinetics

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

Absorption
Following IV or IM injection, parecoxib sodium is rapidly and essentially completely converted to valdecoxib. Exposure [plasma concentration vs. time curve (AUC) and peak concentration (Cmax)] of valdecoxib following injection of parecoxib sodium is approximately linear in the dosage range of clinical doses. Steady state was reached within 4 days with BD dosing.
Following single IV and IM doses of parecoxib sodium 20 mg, C_{max} of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C_{max} following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average C_{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C_{max} of valdecoxib is comparable after IM and IV parecoxib sodium administration.

Distribution
The volume of distribution of valdecoxib after its IV administration is approximately 55 L. Plasma protein binding is about 98% over the concentration range (0.21 – 2.38 mcg/mL) 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. The rate of conversion of parecoxib to valdecoxib is not affected in patients with mild to moderate hepatic impairment. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways. The cytochrome P-450 (CYP-450) dependent pathway involves predominantly 3A4 and 2C9 isozymes while the CYP-450 independent pathway leads to glucuronide conjugates of the sulfonamide moiety.
One active minor metabolite (a hydroxylated form via the CYP-450 pathway) of valdecoxib has been identified in human plasma at approximately 10% the concentration of valdecoxib. It also undergoes extensive metabolism, with <5% of the dose excreted in the urine and faeces. Because of its minor presence, this metabolite is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium

Excretion
Following conversion from parecoxib, valdecoxib is eliminated via hepatic metabolism with <5% of the dose excreted unchanged in the urine. No unchanged parecoxib is detected in urine and only a trace amount in faeces. About 70% of the dose is excreted in the urine as inactive metabolites. The elimination half-life (T1/2) of valdecoxib after IV or IM dosing of parecoxib sodium is about 8 hours. Plasma clearance (CLp) for valdecoxib is about 6 L/hr. In patients undergoing haemodialysis the CLp of valdecoxib was similar to the CLp found in healthy subjects.

Special Populations
Elderly (>65 years)

Parecoxib sodium Injection has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. 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.

Children and Adolescents
Parecoxib sodium Injection has not been investigated in paediatric patients under 18 years of age.

Race
Pharmacokinetic differences due to race have not been identified in clinical and pharmacokinetic studies conducted to date.

Renal Impairment
In patients with varying degrees of renal impairment administered 20 mg IV parecoxib, 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 severe renal impairment or in patients undergoing dialysis.

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 score 7-9), treatment should be initiated with half the usual recommended dose of parecoxib 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 in patients with severe hepatic impairment is not recommended.

INDICATIONS

Management of post-operative pain in the immediate post-operative setting only with the exception of patients undergoing coronary artery bypass grafting (CABG) procedures and in those patients with elevated cardiovascular risk, such as those with congestive heart failure (NYHA II-IV), established ischaemic heart disease and/or cerebrovascular disease.

CONTRAINDICATIONS

PARECOXB Injection is contraindicated in patients:

- undergoing CABG or other major vascular surgery.
- with unstable or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- with known hypersensitivity to parecoxib sodium, valdecoxib or to any other ingredient of the product.
- who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, NSAIDs or other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactoid-like reactions to PARECOXB Injection are possible in such patients (see PRECAUTIONS, Anaphylactoid Reactions and Pre-existing Asthma).
- who have demonstrated allergic-type reactions to sulfonamides (see PRECAUTIONS, Serious Skin Reactions).
- with severe hepatic impairment (Child-Pugh score ≥10; see PHARMACOLOGY and DOSAGE AND ADMINISTRATION)

WARNINGS AND PRECAUTIONS

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see CONTRAINDICATIONS).
Parecoxib Injection has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is limited experience in other types of surgery, for example gastrointestinal or urological surgery
Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.
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. There is limited clinical experience with Parecoxib Injection treatment beyond three days.
If, during treatment, patients deteriorate in any of the organ system functions described below, appropriate measures should be taken and discontinuation of parecoxib therapy should be considered.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is therefore considered essentially 'sodium- free'.

Cardiovascular
COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with parecoxib after careful consideration
Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients. Parecoxib Injection has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft (CABG) procedures. Studies in types of surgery other than CABG procedures included patients with American Society of Anaesthesiology (ASA) Physical Status Class I-III only.

Acetylsalicyclic acid and other NSAIDs
COX-2 inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued. Caution should be exercised when co-administering Parecoxib Injection with warfarin and other oral anticoagulants. The concomitant use of parecoxib with other non- acetylsalicylic acid NSAIDs should be avoided.
Parecoxib Injection may mask fever and other signs of inflammation. 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 Injection. Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Parecoxib Injection.

Gastrointestinal
Upper gastrointestinal (GI) complications (perforations, ulcers or bleedings [PUBs]), some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding, or patients using acetylsalicylic acid concomitantly. The NSAIDs class is also associated with increased GI complications when coadministered with glucocorticoids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or patients ingesting alcohol. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Skin Reactions
Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib. Additionally, fatal reports of toxic epidermal necrolysis have been reported through post-marketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib. DRESS syndrome may occur with parecoxib exposure based on other serious skin reactions reported with celecoxib and valdecoxib exposure.
Patients appear to be at highest risk for these reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment.
Appropriate measures should be taken by physicians 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.
Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors. Patients with a history of sulfonamide allergy may be at greater risk of skin reactions. Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity
Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulfonamides. Parecoxib should be discontinued at the first sign of hypersensitivity.
Cases of severe hypotension shortly following parecoxib administration have been reported in post-marketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The physician should be prepared to treat severe hypotension.

Fluid retention, oedema, renal
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, pre-existing oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken.
Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib. Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Parecoxib Injection in patients with impaired renal function or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.
Caution should be used when initiating treatment with Parecoxib Injection in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Parecoxib Injection.

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

Hepatic impairment
Parecoxib Injection should be used with caution in patients with moderate hepatic impairment (Child-Pugh score 7-9).

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

WARNING
Risk of GI Ulceration, Bleeding and Perforation with NSAID Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy.
Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk.
Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Effects on Ability to Drive and Use Machines
The effect of Parecoxib sodium Injection on ability to drive or use machinery has not been studied. However, patients who experience dizziness, vertigo or somnolence after receiving PARECOXB Injection should refrain from driving or operating machinery.

INTERACTIONS WITH OTHER MEDICINES

Pharmacodynamic interactions
Anticoagulant therapy should be monitored, particularly during the first few days after initiating
Parecoxib Injection therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed (see section on Warnings and Precautions).
Parecoxib Injection had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.
Co-administration of parecoxib and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.
Inhibition of prostaglandins by NSAIDs, including COX-2 inhibitors, may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers and diuretics. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers and diuretics.

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

Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.
Co-administration of NSAIDs and ciclosporin or tacrolimus has been suggested to

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increase the nephrotoxic effect of ciclosporin and tacrolimus because of NSAID effects on renal prostaglandins. Renal function should be monitored when parecoxib and any of these medicinal products are coadministered.
Parecoxib Injection may be co-administered with opioid analgesics.

Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)
Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.
Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib should be reduced in those patients who are receiving fluconazole therapy.
Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole
The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products
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 Injection and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).
Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Parecoxib Injection with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).
In two pharmacokinetic interaction studies in rheumatoid arthritis patients receiving a stable weekly methotrexate dose (5-20 mg/week, as a single oral or intramuscular dose), orally administered valdecoxib (10 mg twice daily or 40 mg twice daily) had little or no effect on the steady-state plasma concentrations of methotrexate. However, caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate. Adequate monitoring of methotrexate-related toxicity should be considered when co-administering parecoxib and methotrexate.
Co-administration of valdecoxib and lithium produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentration should be monitored closely when initiating or changing parecoxib therapy in patients receiving lithium.
Co-administration of valdecoxib with glibenclamide (CYP3A4 substrate) did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

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

Inhalation anaesthetics
No formal interaction studies have been done. In surgery studies in which parecoxib was administered pre-operatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib and the inhalation anaesthetic agents nitrous oxide and isoflurane (see Pharmacodynamic properties).

Fertility, Pregnancy and Lactation

Pregnancy:
Parecoxib sodium is suspected to cause serious birth defects when administered during the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin, it may cause premature closure of the ductus arteriosus or uterine inertia
NSAID use during the second or third trimester of pregnancy may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.
Parecoxib is contraindicated in the third trimester of pregnancy.
There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. During the first and second trimester of pregnancy, Parecoxib Injection should not be given unless clearly necessary.

Lactation:
Parecoxib and its active metabolite are excreted in the milk of lactating rats. Administration of a single dose of parecoxib to lactating women resulted in the transfer of a relatively small amount of parecoxib and its active metabolite into breast milk, and this resulted in a low relative dose for the infant (less than 1% of the weight-adjusted maternal dose). Because of the potential for adverse reactions in nursing infants from parecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility:
The use of parecoxib, as with any medicinal product known to inhibit cyclooxygenase/ prostaglandin synthesis, is not recommended in women attempting to conceive.

ADVERSE EFFECTS

Events occurring ≥10% - Very common
Gastrointestinal disorders: nausea

Events occurring ≥1% and <10% - Common
Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, vomiting
General disorders and administration site conditions: edema peripheral
Infections and infestations: alveolar osteitis (dry socket)
Nervous system disorders: dizziness
Psychiatric disorders: insomnia
Renal and urinary disorders: oliguria
Skin and subcutaneous tissue disorders: sweating increased, pruritus
Vascular disorders: hypotension

Events occurring ≥0.5% and <1% - Uncommon
Gastrointestinal disorders: mouth dry, flatulence
Musculoskeletal and connective tissue disorders: back pain
Cardiac disorders: bradycardia
Infections and infestations: pharyngitis
Skin and subcutaneous tissue disorders: rash
Vascular disorders: hypertension

Events occurring <0.5% - Rare
Cardiac disorders: myocardial infarction
Ear and labyrinth disorders: earache
Gastrointestinal disorders: esophagitis, gastroesophageal reflux, hypoactive bowel sounds,

pancreatitis, perioral swelling
General disorders and administration site conditions: injection site pain, injection site reaction, asthenia
Immune system disorders: anaphylactoid reaction
Investigations: BUN increased, creatine phosphokinase increased, creatinine increase, LDH increased
Injury, poisoning and procedural complications: skin post-operative complications
Metabolism and nutrition disorders: anorexia, hyperglycemia
Musculoskeletal and connective tissue disorders: arthralgia
Nervous system disorders: cerebrovascular disorder
Psychiatric disorders: agitation
Renal and urinary disorders: renal failure acute
Respiratory, thoracic and mediastinal disorders: embolism pulmonary
Skin and subcutaneous tissue disorders: ecchymosis, urticaria
Vascular disorders: hypertension aggravated, hypotension postural
Following coronary artery bypass graft surgery, patients administered parecoxib have a higher risk of adverse events, such as cardiovascular thromboembolic events (e.g., myocardial infarction and cerebrovascular accident), deep surgical infections or sternal wound healing complications.

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Post-Marketing Surveillance
In post-marketing experience, the following rare, serious adverse events have been reported in association with the use of parecoxib: circulatory collapse, erythema multiforme, Stevens-Johnson syndrome, renal failure, and hypersensitivity reactions including anaphylaxis and angioedema.
In post-marketing experience, in addition to *the severe cutaneous adverse reaction* erythema multiforme and Stevens-Johnson's syndrome, toxic epidermal necrolysis has been reported in association with the use of valdecoxib and cannot be ruled out for parecoxib.

DOSAGE AND ADMINISTRATION

"There is limited clinical experience with parecoxib treatment beyond three days."
Parecoxib may be administered as single or multiple IV. or IM. doses on a regular or as needed schedule. After initiation of therapy, dosage should be adjusted based on patient response. Clinical studies with parecoxib were conducted using up to 7 days of treatment. Parecoxib 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 (CV) risk of cyclooxygenase-2 (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. However, the relevance of these findings for the short-term use of parecoxib in the post-operative setting has not been evaluated.

- **Management of Acute Pain:** The recommended single or initial dose for treatment of acute pain is 40 mg, administered either IV. or IM., followed by 20 mg or 40 mg every 6 to 12 hours, as required, up to a maximum daily dosage of 80 mg. The IV bolus injection may be given directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle.
- **Concomitant Use with Opioid Analgesics**: Opioid analgesics can be used concurrently with parecoxib, dosing as described above. In clinical trials, the daily requirement for opioids was significantly reduced (20%-40%) when co-administered with parecoxib. An optimal effect is achieved when parecoxib is given prior to opioid administration. In all clinical assessments, parecoxib was administered at a fixed time interval whereas the opioids were administered on as needed basis (PRN).

Elderly: No dosage adjustment is generally necessary. However, for elderly patients weighing less than 50 kg, it is advisable to reduce the initial dose of parecoxib by 50%. The maximum daily dose should be reduced to 40 mg in elderly patients weighing less than 50 kg.
Hepatic Impairment: No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Treatment with parecoxib should be initiated at the lowest recommended dose in patients with moderate hepatic impairment (Child-Pugh Class B).
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of parecoxib in these patients is not recommended.
Renal Impairment: In patients with severe renal impairment (creatinine clearance <30 mL/minute), or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose and the patient's kidney function closely monitored.
Co-administration with Fluconazole: When parecoxib is co-administered with fluconazole, the lowest recommended dose of parecoxib should be used.
Pediatric Patients: Safety and efficacy have not been established in children under 18 years of age.

Incompatibilities
This medicinal product must **not** be mixed with other medicinal products and should be reconstituted only with sodium chloride solution (0.9% w/v) (provided in some packs) or the diluents mentioned in DOSAGE AND ADMINISTRATION, Instructions for Use and Handling and Disposal.
Use of Lactated Ringer's or 5% Glucose in Lactated Ringer's for reconstitution will cause the medicine to precipitate from solution and therefore is **not** recommended.
Use of Sterile Water for Injections is **not** recommended, as the resulting solution is not isotonic.
Injection into an IV line delivering 5% Glucose in Lactated Ringer's, or other IV fluids not listed in DOSAGE AND ADMINISTRATION, Instructions for Use and Handling and Disposal, is **not** recommended as this may cause precipitation from solution.

Instructions for Use and Handling and Disposal
Reconstitute PARECOXB Injection with 2 mL sodium chloride solution (0.9% w/v) using aseptic technique. The **only** other acceptable diluents for reconstitution are:
5% Glucose Intravenous Infusion
0.45% Sodium Chloride and 5% Glucose Injection.
Use of Sterile Water for Injections is **not** recommended, as the resulting solution is not isotonic.
After reconstitution, PARECOXB Injection should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.
To reduce microbiological hazard, use as soon as practicable after reconstitution. The reconstituted product should **not** be stored in a refrigerator or freezer.
After reconstitution with acceptable diluents, PARECOXB Injection may **only** be injected IV or IM, or into IV lines delivering:

- Sodium Chloride Solution (0.9% w/v)
- 5% Glucose Intravenous Infusion
- 0.45% Sodium Chloride and 5% Glucose Injection\
- Lactated Ringer's.

Injection into IV lines delivering 5% Glucose in Lactated Ringer's, or other IV diluents not listed here, is **not** recommended as this may cause precipitation from solution (see DOSAGE AND ADMINISTRATION, Incompatibilities).
This product contains no antimicrobial agent. PARECOXB Injection is for single use in one patient only. Discard any residue. Any unused product, diluent or waste material should be disposed of according to local requirements.

OVERDOSAGE

Signs and Symptoms
Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, epigastric pain, and other gastrointestinal effects, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Treatment of Overdosage
There are no specific antidotes. Patients should be managed by symptomatic and supportive care following an overdose. Monitor patients for signs and symptoms of gastrointestinal ulceration and/or haemorrhage. Monitor serum electrolytes, renal function and urinalysis after significant overdose.
Valdecoxib is not removed by haemodialysis. Forced diuresis or alkalinisation of urine may not be useful due to high protein binding of valdecoxib.

PRESENTATION AND STORAGE CONDITIONS

Parecoxib Sodium Vials
Glass vial with a sterilized, lyophilizing rubber stopper; sealed with a flip-off cap on the aluminium overseal.
PARECOXB parecoxib (as sodium) 40mg powder for solution for injection.
Pack without Diluent : 5s or 10s glass vial with parecoxib 40mg.
Pack with Diluent: 5s or 10s glass vial with parecoxib 40mg and 5s or 10s Ampoules of Diluent Sodium Chloride 0.9% w/v.
(Not all packs will be available)

Storage
Parecoxib: This medicinal product has to be stored below 30°C prior to reconstitution.

Diluent Sodium Chloride Infusion (0.9% w/v) : Store below 30°C

Storage conditions of the reconstituted medicinal product: From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and the conditions prior to use are the responsibility of the user.

Store below 30°C. Protect from light. Do not freeze before or after dilution.

Shelf Life:
Parecoxib: 36 months.
Diluent Sodium Chloride Infusion (0.9% w/v): 36 months

NAME AND ADDRESS OF THE PRODUCT REGISTRATION HOLDER

UNIMED SDN BHD
53, Jalan Tembaga SD 5/2B,
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REGISTRATION NUMBER

MAL21036025ACZ

DATE OF PREPARATION

April 2023

PARECOXB Leaflet Malaysia
Dimensions: 120 mm x 350 mm
Font: Arial Narrow
Font Size: 4.85 pt