



## 1. NAME OF MEDICINAL PRODUCT

**Parecam 40mg Powder for Solution for Injection**  
**Parecam 40mg Powder and Solvent for Solution for Injection**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg parecoxib (present as 42.36 mg parecoxib sodium) for reconstitution with 2 mL of solvent. After reconstitution, the final concentration of parecoxib is 20 mg/mL.

When reconstituted in 0.9% sodium chloride injection, Parecam contains approximately 0.44 mEq of sodium per vial.

## 3. PHARMACEUTICAL FORM

Before reconstitute: White to off-white lyophilized cake or powder.

After reconstitute: Clear, colourless solution, free from visible particulates.

Solvent: Clear colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic 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.

### 4.2 Posology and Method of 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.

### 4.3 Contraindication

Parecoxib is contraindicated in:

- Patients with known hypersensitivity to parecoxib or to any of the excipients of the product.
- Patients who have demonstrated allergic-type reactions to sulfonamides.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after

taking acetylsalicylic acid (aspirin) or non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.

- Severe hepatic impairment (serum albumin <25 g/L or Child-Pugh score ≥10).
- The third trimester of pregnancy and breast-feeding.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Treatment of post-operative pain following coronary artery bypass graft (CABG) surgery.
- Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

### 4.4 Special Warnings and Precautions for Use

#### Administration Other than IV or IM

Modes of administration other than IV or IM have not been studied and should not be used.

#### Cardiovascular Effects

COX-2 inhibitors, of which parecoxib is one, have been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long-term. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known cardiovascular disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. 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.

Two separate studies in coronary artery bypass graft (CABG) surgery showed that patients receiving parecoxib for a minimum of 3 days followed by oral valdecoxib (the active metabolite of parecoxib) for 7 to 14 days, had increased incidence of cardiovascular/thromboembolic events (e.g., myocardial infarction and cerebrovascular accident) compared to those receiving placebo. Parecoxib is therefore, contraindicated for the treatment of post-operative pain immediately following CABG surgery.

#### Gastrointestinal (GI) Effects

Upper gastrointestinal (GI) perforations, ulcers, or bleeds have occurred in patients treated with parecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, or patients with a history of, or active, GI disease, such as ulceration, bleeding, or inflammatory conditions; or patients using concomitant aspirin. The NSAIDs class is also associated with increased GI complications when co-administered with corticosteroids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or patients ingesting alcohol, however, there are currently no specific parecoxib clinical data.

#### Skin Effects

Valdecoxib, the active moiety of parecoxib, contains a sulfonamide moiety and patients with a known history of a sulfonamide allergy may be at a greater risk of skin reactions. Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Serious skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported through post-marketing surveillance in patients receiving parecoxib. In addition to erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis has been reported through post-marketing surveillance in patients receiving valdecoxib. Fatalities due to Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with valdecoxib and the potential cannot be ruled out for parecoxib. Some NSAIDs and selective COX-2 inhibitors have been associated with an increased risk of generalized bullous fixed drug eruption (GBFDE). Drug reaction with eosinophilia and systemic symptoms syndrome (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 events early in the course of therapy, with the onset of the event occurring in the majority of cases within the first two weeks of treatment. Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity. Serious skin reactions have been reported with other COX-2 inhibitors during post-marketing experience. The reported rate of these events appears to be greater for valdecoxib as compared to other COX-2 agents.

#### Anaphylactoid Reactions

Hypersensitivity reactions (anaphylactic reactions and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib. These reactions have occurred in patients with and without a history of allergic-type reactions to sulfonamides.

#### Severe Hypotension

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 practitioner should be prepared to treat severe hypotension.

#### 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).

Co-administration of parecoxib with warfarin caused a small increase in the AUC of warfarin, and also in the prothrombin time (measured by International Normalized Ratio [INR]). While mean INR values were only slightly increased with co-administration of parecoxib, the day-to-day variability in individual INR values was increased. Anticoagulant activity should be monitored, particularly during the first few days after initiating parecoxib, in patients receiving warfarin or similar agents, since these patients may be at increased risk of bleeding complications.

#### 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. NSAIDs, including 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

#### Fluid retention and Oedema

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

#### Renal Effects

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib. Renal function should be closely monitored in patients with advanced renal disease who are administered parecoxib.

Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with parecoxib.

#### Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of parecoxib in patients with severe hepatic impairment is not recommended. Parecoxib should be used with caution when treating patients with moderate hepatic impairment (ChildPugh Class B), and initiated at the lowest recommended dose.

A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with parecoxib.

#### General

By reducing inflammation, parecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections. The concomitant use of parecoxib with other non-specific NSAIDs should be avoided.

### 4.5 Interaction With Other Medicinal Products and Other Forms of Interaction

#### General

The drug interaction studies were performed with either parecoxib or the active moiety (valdecoxib).

In humans, parecoxib undergoes extensive hepatic metabolism involving P450 isoenzymes 3A4 and 2C9, and non-P450 dependent pathways (i.e., glucuronidation). Concomitant administration of parecoxib with known CYP 3A4 and 2C9 inhibitors can result in increased AUC of parecoxib.

#### Drug-specific

*Interaction of parecoxib with warfarin or similar agents:* See Special Warnings and Precautions for Use.

*Fluconazole and ketoconazole:* Co-administration of fluconazole, a CYP2C9 inhibitor, and ketoconazole, a CYP3A4 inhibitor, enhanced the AUC of valdecoxib by 62% and 38%, respectively. When parecoxib is co-administered with fluconazole, the lowest recommended dose of parecoxib should be used. No dosage adjustment is necessary when parecoxib is co-administered with ketoconazole.

*Anti-hypertensives including ACE-inhibitors, angiotensin II antagonists, beta blockers and diuretics:* Inhibition of prostaglandins 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 and/or angiotensin II antagonists, may result in 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.

*Diuretics:* Clinical studies have shown that NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

*Cyclosporine:* Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporine.

*Methotrexate:* A pharmacokinetic interaction study was conducted using valdecoxib and methotrexate and no clinically important interactions were seen. However, caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate.

*Lithium:* Valdecoxib produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) resulting in a 34% higher serum AUC compared to lithium alone. Lithium serum concentrations should be monitored closely when initiating or changing parecoxib therapy in patients receiving lithium.

*Other:* Interaction studies were conducted between parecoxib and I.V. or oral midazolam, heparin, propofol, fentanyl, and alfentanil. Interaction studies were also conducted between valdecoxib and glibenclamide (glyburide), oral contraceptives (ethinyl estradiol/norethindrone), phenytoin, omeprazole and diazepam. No clinically important interactions were seen in these studies.

Parecoxib may be co-administered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when co-administered with parecoxib.

No formal interaction studies were performed with parecoxib and inhalation anesthetic agents, such as nitrous oxide and isoflurane; however, no evidence of a drug interaction was observed in clinical studies.

Parecoxib does not interfere with the anti-platelet effect of low-dose aspirin. Because of its lack of platelet effects, parecoxib is not a replacement for aspirin in the prophylactic treatment of cardiovascular disease.

### 4.6 Fertility, Pregnancy and Lactation

#### Pregnancy

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

Parecam 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. Previous data suggested that there is an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, Parecam should not be given unless clearly necessary.

#### Lactation

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.

Based on the mechanism of action, the use of NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including Parecam should be considered.

### 4.7 Effects on Ability to Drive and Use Machines

The effect of parecoxib on ability to drive or use machinery has not been studied.

### 4.8 Undesirable Effects

Clinical Trials.

The following adverse reactions were reported in patients who received parecoxib (N = 5,402) in 28 placebo-controlled clinical trials.

#### Events occurring ≥10%

Gastrointestinal disorders: nausea

#### Events occurring ≥1% and <10%

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%

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
<b>Events occurring &lt;0.5%</b>
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., 10myocardial infarction and cerebrovascular accident), deep surgical infections or sternal wound healing complications.

#### 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.

#### 4.9 Overdose

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

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

#### 5. PHARMACOLOGICAL PROPERTIES

##### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anti-inflammatory and Antirheumatic Products, Non-Steroids, Coxibs, ATC Code: M01AH04.

Parecoxib is a prodrug of valdecoxib. Valdecoxib is an NSAID that exhibits anti-inflammatory, analgesic and antipyretic properties in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2). At therapeutic plasma concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

Based on reported data, parecoxib has been studied in a broad range of major and minor surgeries. The efficacy of parecoxib was established in studies of dental, gynaecologic (hysterectomy), orthopaedics (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 to 13 minutes, with clinically meaningful analgesia demonstrated in 23 to 39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg parecoxib. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose-dependent, and the clinical pain model ranged from 6 to more than 12 hours.

##### Use of Parecoxib Beyond 3 Days

Most trials were designed for dosing up to 3 days. Data from 3 of 28 randomized placebo controlled trials, where the protocols allowed treatment of parecoxib for >3 days was pooled and analyzed, 358 patients received parecoxib for >3 days and 318 patients received placebo for >3 days. Both groups had similar demographics. The mean (SD) 10duration of treatment was 4.1 (0.4) days for parecoxib and 4.2 (0.5) days for placebo, the range was 4 to 7 days for parecoxib and 4 to 9 days for placebo. The occurrence of AE in patients receiving parecoxib for 4 to 7 days (median duration 4 days) was low after treatment Day 3 and similar to placebo.

#### Opioid-Sparing Effects

Parecoxib, at recommended doses, significantly reduced opioid consumption and patient reported opioid-related adverse effects (fatigue, drowsiness, confusion, inability to concentrate, dizziness, nausea, constipation, difficult urination, itching, retching/vomiting), while providing improved pain relief compared to opioids alone.

In a placebo-controlled, orthopedic and general surgery study (n = 1050), patients received parecoxib at an initial parenteral dose of 40 mg IV followed by 20 mg twice daily for a minimum of 72 hours in addition to receiving standard care including supplemental patient controlled opioids (IV morphine sulfate). The reduction in opioid use with parecoxib treatment on Days 2 and 3 was 7.2 mg and 2.8 mg (37% and 28% respectively). This reduction in opioid use was accompanied by significant reductions in patient-reported opioid symptom distress, as well as improved pain relief compared to opioids alone. Additional studies in other surgical settings provided similar observations.

#### Gastrointestinal studies

In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (>65 years) subjects administered parecoxib (5%-21%), although higher than placebo (5%-12%), was statistically significantly lower than the incidence observed with NSAIDs (66%-90%).

#### Coronary Artery Bypass Surgery (CABG) Post-Operative Safety Studies

In addition to routine adverse event reporting, pre-specified event categories, adjudicated by an independent expert committee, were examined in two placebo-controlled safety studies in which patients received parecoxib sodium for at least 3 days and then were transitioned to oral valdecoxib for a total duration of 10 to 14 days. All patients received standard of care analgesia during treatment.

Patients received low-dose acetylsalicylic acid prior to randomization and throughout the two CABG surgery studies.

The first CABG surgery study evaluated patients treated with IV parecoxib sodium 40 mg twice daily for a minimum of 3 days, followed by treatment with valdecoxib 40 mg twice daily (parecoxib sodium/valdecoxib group) (n = 311) or placebo/placebo (n = 151) in a 14-day, double-blind placebo-controlled study. Nine pre-specified adverse event categories were evaluated (cardiovascular thromboembolic events, pericarditis, new onset or exacerbation of congestive heart failure, renal failure/dysfunction, upper GI ulcer complications, major non-GI bleeds, infections, non-infectious pulmonary complications, and death). There was a significantly (p < 0.05) greater incidence of cardiovascular/thromboembolic events (myocardial infarction, ischemia, cerebrovascular accident, deep vein thrombosis and pulmonary embolism) detected in the parecoxib/valdecoxib treatment group compared to the placebo/placebo treatment group for the IV dosing period (2.2% and 0.0% respectively) and over the entire study period (4.8% and 1.3% respectively). Surgical wound complications (most involving the sternal wound) were observed at an increased rate with parecoxib/valdecoxib treatment.

In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib initial dose of 40 mg IV, then 20 mg IV every 12 hours for a minimum of 3 days followed by valdecoxib PO (20 mg every 12 hours) (n = 544) for the remainder of a 10 day treatment period; placebo IV followed by valdecoxib PO (n = 544); or placebo IV followed by placebo PO (n = 548). A significantly (p = 0.033) greater incidence of events in the cardiovascular/thromboembolic category was detected in the parecoxib/valdecoxib treatment group (2.0%) compared to the placebo/placebo treatment group (0.5%). Placebo/valdecoxib treatment was also associated with a higher incidence of CV thromboembolic events versus placebo treatment, but this difference did not reach statistical significance. Three of the six cardiovascular thromboembolic events in the placebo/valdecoxib treatment group occurred during the placebo treatment period; these patients did not receive valdecoxib. Pre-specified events that occurred with the highest incidence in all three treatment groups involved the category of surgical wound complications, including deep surgical infections and sternal wound healing events.

There were no significant differences between active treatments and placebo for any of the other pre-specified event categories (renal dysfunction/failure, upper GI ulcer complications or surgical wound complications).

Parecoxib has not been studied in cardiovascular revascularization procedures other than CABG.

##### General Surgery

In a large (N = 1050) major orthopedic/general surgery trial, patients received an initial dose of parecoxib 40 mg IV, then 20 mg IV every 12 hours for a minimum of 3 days followed by valdecoxib PO (20 mg every 12 hours) (n = 525) for the remainder of a 10 day treatment period, or placebo IV followed by placebo PO (n = 525). There were no significant differences in the overall safety profile, including the four pre-specified event categories described above for the second CABG surgery study, for parecoxib sodium/valdecoxib compared to placebo treatment in these post-surgical patients.

#### Platelet Studies

In a series of small, multiple dose studies in healthy young and elderly subjects, parecoxib 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, parecoxib 40 mg twice daily had no clinically

significant effect on acetylsalicylic acid - mediated inhibition of platelet function.

#### 5.2 Pharmacokinetic Properties

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

#### Absorption

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

Following single IV and IM doses of parecoxib sodium 20 mg, Cmax of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and Cmax following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average Cmax 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 Cmax 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 litres. 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 and propionic acid 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 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) 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; 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.

#### Elimination

Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib 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 (t1/2) of valdecoxib is about 8 hours.

#### Elderly

Based on available data, parecoxib 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.

#### 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 Class B), 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..

#### 6. PHARMACEUTICAL PARTICULARS

##### 6.1 List of excipients

Disodium Hydrogen Orthophosphate

Ortho Phosphoric Acid

Sodium Hydroxide

Water for Injection

This medicinal product contains less than 1mmol sodium (23 mg) per dose, that is to say essentially `sodium-free`.

#### 6.2 Incompatibilities

Following reconstitution with an acceptable diluent, parecoxib sodium may be injected into an IV line delivering 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Lactated Ringers Injection, or 5% Dextrose and 0.45% Sodium Chloride Injection. Injection into a line delivering

5% Dextrose in Lactated Ringer’s, or other IV fluid not listed here, is not recommended, as this may cause precipitation from solution.

Parecoxib sodium should not be admixed for injection with any other drug.

Do not inject parecoxib into an IV line delivering any other drug. The IV line must be adequately flushed prior to, and after parecoxib injection with a solution of known compatibility.

#### 6.3 Shelf Life

Please refer to outer carton for expiry date.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 12 hours at 30°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

#### 6.4 Special Precautions for storage

Store below 30°C.

Do not refrigerate or freeze reconstituted solutions.

For storage conditions of the reconstituted medicinal product see section 6.3 Shelf-life

#### 6.5 Nature and Contents of Container

Pack of 1: Powder and Solvent for Solution for Injection
1 x 6mL vial (clear glass) of 40mg Powder for Solution for Injection and 1 x 2mL ampoule (clear glass) of Solvent for Solution for Injection. 1 vial and 1 ampoule packed in paper carton.

Pack of 10: Powder for Solution for Injection
10 x 6mL vial (clear glass) of 40mg Powder for Solution for Injection. 10 vials per unit PVC tray were packed in paper carton.

#### 6.6 Special Precautions for Disposal and Other Handling

Parecoxib sodium for injection is a preservative-free lyophilized powder. Parecoxib sodium should be reconstituted with 2mL (40mg vial) of the provided solvent sodium chloride injection (0.9%).

Alternatively, parecoxib sodium may be reconstituted with 2mL bacteriostatic 0.9% Sodium Chloride Injection, 5% Dextrose Injection or 5% Dextrose and 0.45% Sodium Chloride Injection.

Use of Lactated Ringer’s Injection, or 5% Dextrose in Lactated Ringer’s Injection, are not recommended for reconstitution as they will cause the drug to precipitate from solution. Use of Water for Injection is not recommended for reconstitution of parecoxib sodium, as the resulting solution is not isotonic.

Do not refrigerate or freeze the reconstituted product.

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

#### PRODUCT REGISTRATION HOLDER/ MANUFACTURER

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