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PARECOXIB

DYNASTAT®

40 mg Lyophilized Powder for IM/IV Injection

Absolute contraindications:

Not be given to those patients who have history of:

- Stroke: cerebrovascular accident, CVA
- Heart attack: Myocardial infarction, MI
- Coronary artery bypass graft, CABG
- Uncontrolled hypertension
- Congestive heart failure, (CHF) NYHA II - IV

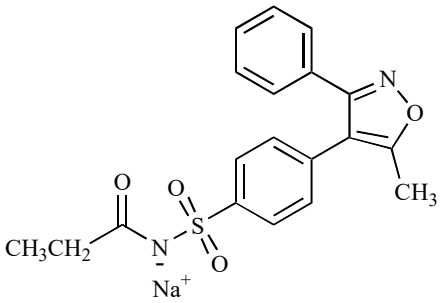
1.0 PHARMACOLOGIC CATEGORY

Selective COX-2 Inhibitor.

2.0 DESCRIPTION

Parecoxib sodium (hereafter referred to as parecoxib) is the prodrug for the pharmacologically active moiety, valdecoxib. Following injection, parecoxib (Dynastat) is rapidly and completely hydrolyzed enzymatically to valdecoxib.

Parecoxib (Dynastat) is chemically designated: N-[[4-(5-methyl-3-phenyl-4 isoxazolyl)phenyl]sulfonyl] propanamide, sodium salt. It has the following chemical structure:



$C_{19}H_{17}N_2O_4SNa$ M.W. = 392.41
CAS registry no: 198470-85-8

Parecoxib (Dynastat) 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.

3.0 FORMULATION/COMPOSITION

Parecoxib (Dynastat) 40 mg vial:
Drug: Each vial contains Parecoxib (as sodium)..... 40 mg
Diluent: Each 2 mL ampoule contains Sodium Chloride..... 0.9%

For reconstitution with 2 mL of solvent. After reconstitution, the final concentration of parecoxib (Dynastat) is 20 mg/mL.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the short-term treatment of acute pain and post-operative pain i.e., oral surgery, abdominal hysterectomy, myomectomy, total knee replacement, total hip arthroplasty, laparoscopic cholecystectomy, inguinal hernia repair and other general surgery like diagnostic laparoscopy, gastrectomy, hernioplasty, appendectomy, hemithyroidectomy and splenectomy.

It may be used pre-operatively to prevent or reduce post-operative pain and it can reduce opioid requirements when they are used concomitantly.

The decision to prescribe a selective COX–2 inhibitor should be based on an assessment of the individual patients' overall risks.

4.2 Dosage and Method of Administration

Parecoxib (Dynastat) 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 (Dynastat) were conducted using up to 7 days of treatment.

Parecoxib (Dynastat) 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 (Dynastat) 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.

Prevention or Reduction of Post-operative Pain
The recommended dose is 40 mg administered IV or IM (but preferably IV) 30 to 45 minutes prior to surgical incision. Continued medication with parecoxib (Dynastat) post-operatively may be needed for adequate analgesic effect.

Concomitant Use with Opioid Analgesics
Opioid analgesics can be used concurrently with parecoxib (Dynastat), dosing as described above. In clinical trials, the daily requirement for opioids was significantly reduced (20%-40%) when co-administered with parecoxib (Dynastat). An optimal effect is achieved when parecoxib (Dynastat) is given prior to opioid administration. In all clinical assessments parecoxib (Dynastat) 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 (Dynastat) 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 (Dynastat) 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 (Dynastat) 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 (Dynastat) should be initiated at the lowest recommended dose and the patient's kidney function closely monitored.

Co-administration with Fluconazole: When parecoxib (Dynastat) is co-administered with fluconazole, the lowest recommended dose of parecoxib (Dynastat) should be used.

Pediatric Patients: Safety and efficacy have not been established in children under 18 years of age.

4.3 Contraindications

Parecoxib is contraindicated in:

- Patients with known hypersensitivity to parecoxib (Dynastat) or to any other ingredient of the product.
- Patients who have demonstrated allergic-type reactions to sulfonamides.
- Patients with history of previous serious allergic drug 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 (**see sections 4.4 – Special Warnings and Precautions for Use** and **4.8 – Undesirable Effects**).
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, bronchial asthma, angioneurotic edema, urticaria or other allergic-type reactions after taking acetylsalicylic acid (aspirin) or non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- The third trimester of pregnancy and breast-feeding (**see sections 4.6 – Fertility, Pregnancy and Lactation** and **5.3 – Preclinical Safety Data**).
- Patients with severe hepatic impairment (serum albumin <25 g/l or Child-Pugh Class C).
- Patients with inflammatory bowel disease.
- Patients with congestive heart failure (NYHA II-IV).
- Treatment of post-operative pain immediately following coronary artery bypass graft (CABG) surgery (**see sections 4.8 – Undesirable Effects** and **5.1 – Pharmacodynamic Properties**).

- Patients with established ischemic 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 (e.g., intra-articular, intrathecal) have not been studied and should not be used.

Cardiovascular Effects
COX-2 inhibitors, of which parecoxib (Dynastat) 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 (Dynastat) for a minimum of 3 days followed by oral valdecoxib (the active metabolite of parecoxib (Dynastat)) for 7 to 14 days, had increased incidence of cardiovascular/thromboembolic events (e.g., myocardial infarction and cerebrovascular accident) compared to those receiving placebo (**see section 5.1 – Pharmacodynamic Properties**). Parecoxib (Dynastat) 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 (Dynastat). 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 (Dynastat), 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 (Dynastat). 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 (Dynastat). Generalized bullous fixed drug eruption (GBFDE) may occur with parecoxib exposure based on a reaction with etoricoxib exposure. 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 (Dynastat) 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 (Dynastat) (**see section 4.8 – Undesirable Effects – Post-marketing Surveillance**). These reactions have occurred in patients with and without a history of allergic-type reactions to sulfonamides (**see section 4.3 – Contraindications**).

Severe Hypotension
Cases of severe hypotension shortly following parecoxib (Dynastat) administration have been reported in post-marketing experience with parecoxib (Dynastat). 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 (Dynastat) 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 (Dynastat), 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 (Dynastat), in patients receiving warfarin or similar agents, since these patients may be at increased risk of bleeding complications.

Hypertension
As with all NSAIDs, parecoxib (Dynastat) 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 (Dynastat), should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with parecoxib (Dynastat) and throughout the course of therapy.

Fluid Retention and Edema
As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking parecoxib (Dynastat). Therefore, parecoxib (Dynastat) 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 (Dynastat) (**see section 4.8 – Undesirable Effects**). Renal function should be closely monitored in patients with advanced renal disease who are administered parecoxib (Dynastat) (**see section 4.2 – Dosage and Method of Administration**).

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

Hepatic Effects
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of parecoxib (Dynastat) in patients with severe hepatic impairment is not recommended. Parecoxib (Dynastat) should be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class B), and initiated at the lowest recommended dose (**see section 4.2 – Dosage and Method of Administration**).

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 (Dynastat).

General
By reducing inflammation, parecoxib (Dynastat) may diminish the utility of diagnostic signs, such as fever, in detecting infections. The concomitant use of parecoxib (Dynastat) 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 (Dynastat) or the active moiety (valdecoxib).

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

Drug-specific
Interaction of parecoxib (Dynastat) with warfarin or similar agents: **See section 4.4 – 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 (Dynastat) is co-administered with fluconazole, the lowest recommended dose of parecoxib (Dynastat) should be used. No dosage adjustment is necessary when parecoxib (Dynastat) is co-administered with ketoconazole (**see section 4.2 – Dosage and Method of Administration**).

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 (Dynastat) 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 (Dynastat) therapy in patients receiving lithium.

Other: Interaction studies were conducted between parecoxib (Dynastat) and IV 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 (Dynastat) may be co-administered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when co-administered with parecoxib (Dynastat).

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

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

4.6 Fertility, Pregnancy and Lactation

Fertility

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 parecoxib (Dynastat), should be considered.

Pregnancy

There are no studies in pregnant women.

Parecoxib (Dynastat) should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

As with other drugs known to inhibit prostaglandin synthesis, use of parecoxib (Dynastat) during the third trimester of pregnancy should be avoided because it may cause uterine inertia

and premature closure of the ductus arteriosus.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss (**see section 5.3 – Preclinical Safety Data**).

If used during second or third trimester of pregnancy, NSAIDs may cause fetal 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 parecoxib should be closely monitored for amniotic fluid volume.

Lactation
Administration of a single dose of parecoxib (Dynastat) to lactating women resulted in the transfer of a relatively small amount of parecoxib (Dynastat) 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 (Dynastat), 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.

4.7 Effects on Ability to Drive and Use Machines

The effect of parecoxib (Dynastat) 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 (Dynastat) (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, pruritis
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

Events occurring <0.5%

Cardiac disorders: myocardial infarction
Ear and labyrinth disorders: earache
Gastrointestinal disorders: esophagitis, gastroesophageal reflux, hypoactive bowel sounds, pancreatitis, peri-oral 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 (Dynastat) 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.

Post-marketing Surveillance

In post-marketing experience, the following rare, serious adverse events have been reported in association with the use of parecoxib (Dynastat): circulatory collapse, erythema multiforme, Stevens-Johnson syndrome, renal failure, and hypersensitivity reactions including anaphylaxis and angioedema (**see section 4.4 – Special Warnings and Precautions for Use**).

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 (Dynastat).

4.9 Overdose and Treatment

Clinical experience of overdose is limited. Single IV doses of up to 200 mg parecoxib (Dynastat) have been administered to healthy subjects without clinically significant adverse effects. Parecoxib (Dynastat) doses of 50 mg IV twice daily (100 mg/day) for 7 days did not result in any signs of toxicity.

In case of suspected acute overdose, appropriate supportive and symptomatic medical care should be provided. There are no specific antidotes. Dialysis is unlikely to be an efficient method of drug removal, because of high protein binding of the drug.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Parecoxib (Dynastat) 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

COX-2. At therapeutic plasma concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

Clinical Studies
Parecoxib has been studied in a broad range of major and minor surgeries. The efficacy of parecoxib (Dynastat) was established in studies of dental, gynecologic (hysterectomy), orthopedic (knee and hip replacement), and coronary artery bypass graft surgical pain (**see section 4.3 – Contraindications**). 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 IV or IM parecoxib (Dynastat). 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 and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

Use 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) duration 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 (Dynastat), 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 (Dynastat) 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 (Dynastat) 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.

Platelets
In clinical trials studying young (18-55 years) and elderly (65-83 years) adult subjects, single and multiple doses up to 7 days of parecoxib (Dynastat) 20 mg and 40 mg twice daily, had no effect on platelet aggregation or bleeding time. By comparison, ketorolac 15 mg and 30 mg as a single dose, or after 5 days treatment, significantly reduced platelet aggregation and significantly increased bleeding time. Parecoxib (Dynastat) (40 mg twice daily) did not have a clinically significant effect on aspirin-mediated inhibition of platelet function, and did not alter the pharmacodynamic effects of heparin on aPTT or platelets, compared to placebo.

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 (Dynastat) (5%-21%), although higher than placebo (5%-12%), was statistically significantly lower than the incidence observed with NSAIDs (66%-90%).

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 (Dynastat) 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 (Dynastat) 40 mg twice daily for a minimum of 3 days, followed by treatment with valdecoxib 40 mg twice daily (parecoxib/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 (Dynastat) 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 (Dynastat) has not been studied in cardiovascular revascularization procedures other than CABG.

In an analysis of 17 controlled trials in non-cardiac major surgery, where the majority of patients were treated for 2 days, patients receiving parecoxib (Dynastat) did not experience an increased risk of cardiovascular adverse events compared to placebo. This included patients with none, one or two cardiovascular risk factors. This analysis has about 77% power to detect

a doubling in the background rate of cardiovascular adverse events in patients treated with parecoxib (Dynastat).

General Surgery
In a large (N=1050) major orthopedic/general surgery trial, patients received an initial dose of parecoxib (Dynastat) 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/valdecoxib compared to placebo treatment in these post-surgical patients.

5.2 Pharmacokinetic Properties

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

Absorption

Exposure of valdecoxib following single doses of parecoxib (Dynastat), 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 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 (Dynastat) 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 (Dynastat) was similar after IV or IM administration in terms of AUC. Average C_{max} of parecoxib (Dynastat) 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 (Dynastat) administration.

Distribution

The volume of distribution of valdecoxib after its IV administration is approximately 55 liters. Plasma protein binding is approximately 98% over the concentration range achieved with the highest recommended dose, 80 mg/day. Valdecoxib, but not parecoxib (Dynastat), is extensively partitioned into erythrocytes.

Metabolism

Parecoxib (Dynastat) 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 sulfonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10% of the concentration of valdecoxib; because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib (Dynastat).

Elimination

Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib recovered in the urine. No unchanged parecoxib (Dynastat) is detected in urine and only trace amounts in the feces. About 70% of the dose is excreted in the urine as inactive metabolites. Plasma clearance (CL_p) for valdecoxib is about 6 l/hour. After IV or IM dosing of parecoxib (Dynastat), the elimination half-life ($t_{1/2}$) of valdecoxib is about 8 hours.

5.3 Preclinical Safety Data

There were no findings of teratogenicity in studies in rats and rabbits. Studies in rats at maternally toxic doses and studies in rabbits at the maximal evaluable dose have not revealed embryotoxic effects other than post-implantation loss, which has been observed with other drugs that inhibit prostaglandin synthesis.

Parecoxib and its active metabolite are excreted in the milk of lactating rats.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2 – fold the maximum human exposure to parecoxib (Dynastat). However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib (Dynastat)) were approximately 0.8 – fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and fetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib (Dynastat) on male or female fertilities were found in rats.

The effects of parecoxib (Dynastat) have not been evaluated in late pregnancy or in the pre- and post-natal period.

Parecoxib (Dynastat) administered intravenously to lactating rats as a single dose showed concentrations of parecoxib (Dynastat), valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib (Dynastat) has not been evaluated.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Dibasic Sodium Phosphate, Anhydrous
Phosphoric Acid, Concentrated
Sodium Hydroxide
Water for Injections
Nitrogen

6.2 Shelf-Life

Please see outer package for the expiry date of the product.

6.3 Storage Conditions

Store drug product and diluent at temperature not exceeding 30°C.
Do not refrigerate or freeze.

6.4 Availability

40 mg Lyophilized Powder for IM/IV Injection: One box contains EP Type I clear glass vial with bromobutyl rubber stopper in blister pack x 5's (as active) + EP Type I clear ampoule of 2 mL in blister pack x 5's (as diluent – 0.9% Sodium Chloride).

6.5 Incompatibilities

Following reconstitution with an acceptable diluent, parecoxib (Dynastat) 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 (Dynastat) should not be admixed for injection with any other drug.

Do not inject parecoxib (Dynastat) into an IV line delivering any other drug. The IV line must be adequately flushed prior to, and after parecoxib (Dynastat) injection with a solution of known compatibility (**see section 6.5 – Special Precautions for Disposal and Other Handling**).

6.6 Special Precautions for Disposal and Other Handling

Parecoxib (Dynastat) is a preservative-free lyophilized powder. Parecoxib (Dynastat) should be reconstituted with 1 mL (20 mg vial) or 2 mL (40 mg vial) Sodium Chloride Injection (0.9%).

Alternatively, parecoxib (Dynastat) may be reconstituted with 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 (Dynastat), as the resulting solution is not isotonic.

Do not refrigerate or freeze the reconstituted product.

Reconstitution Process

Use aseptic technique to reconstitute lyophilized parecoxib (Dynastat).

Remove the purple flip off cap to expose the central portion of the rubber stopper of the 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, parecoxib (Dynastat) should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter is observed. Parecoxib (Dynastat) should be administered within 24 hours of reconstitution, or discarded.

The reconstituted product is isotonic.

7.0 FDA REGISTRATION NUMBER

40 mg Lyophilized Powder for IM/IV Injection: DR-XY27928

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

40 mg Lyophilized Powder for IM/IV Injection: 11 October 2002

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
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Diluent Manufactured by:
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