NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DYNASTAT® (40 mg Powder for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DYNASTAT Injection contains 40 mg parecoxib (as 42.36 mg parecoxib sodium). 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. After reconstitution, the concentration of parecoxib is 20 mg/mL.

Excipient(s) with Known Effect

When reconstituted in sodium chloride solution (0.9% w/v), DYNASTAT Injection contains approximately 0.44 mEq of sodium per 40 mg vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Injection and Powder and Diluent for Injection

DYNASTAT Injection is a white to off-white, preservative-free, lyophilised powder in a single-use vial. For intravenous (IV) or intramuscular (IM) administration, DYNASTAT Injection should be reconstituted with 2 mL sodium chloride solution (0.9% w/v), or a suitable alternative (see section 4.2).

Diluent for Injection

DYNASTAT Injection may be supplied with a 2 mL capacity diluent ampoule with a fill volume of 2 mL Sodium Chloride Intravenous Infusion (0.9% w/v) BP.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For a single peri-operative dose for the management of post-operative pain.

The decision to prescribe DYNASTAT should be based on an assessment of the individual patient's overall risks and the potential risk/benefit profile of alternative parenteral therapies.

As the cardiovascular risks of the selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

4.2 Dose and method of administration

Dose

The usual recommended dose is a single 40 mg dose administered intravenously (IV) or intramuscularly (IM).

Elderly

No dosage adjustment is generally necessary. However, for elderly female patients weighing less than 50 kg, the recommended dose of DYNASTAT Injection is 20 mg (see section 4.4, Use in the Elderly and section 5.2, Special Populations, Elderly (>65 years)).

Hepatic Impairment

No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce DYNASTAT Injection with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore the use of DYNASTAT Injection is contraindicated in these patients (see section 4.3 and section 5.2, Special Populations, Hepatic Impairment.

Renal Impairment

On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate (creatinine clearance of 30-80 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment. However, caution should be observed in patients with severe renal impairment or patients who may be predisposed to fluid retention (see section 4.4 and section 5.2, Special Populations, Renal Impairment).

Paediatric Population

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

Method of Administration

The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle. For instructions on reconstitution of the medicine before administration, see section 6.6.

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 section 6.6.

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 section 6.6 is **not** recommended as this may cause precipitation from solution.

4.3 Contraindications

DYNASTAT Injection is contraindicated in patients:

- undergoing cardiac or major vascular surgery.
- who have previously had a myocardial infarction or stroke.
- 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 DYNASTAT Injection are possible in such patients (see section 4.4, Anaphylactoid Reactions and Pre-existing Asthma).
- who have demonstrated allergic-type reactions to sulfonamides (see section 4.4, Allergic Reactions).
- with severe hepatic impairment (Child-Pugh score ≥10; see sections 5.2 and 4.2).

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

Use of COX-2 inhibitors (of which parecoxib is one) has been associated with an increased risk of cardiovascular (CV) adverse events (myocardial infarction and stroke) (see section 5.1). 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.

Patients treated with parecoxib for pain following CABG surgery have a higher risk of cardiovascular/thromboembolic events (e.g. myocardial infarction and cerebrovascular accident), deep surgical infections, or sternal wound healing complications. Parecoxib is therefore contraindicated for the treatment of post-operative pain immediately following cardiac surgery. It may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Patients with significant risk factors for cardiovascular

events should only be treated with parecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies. Prescribers should inform the individual patient of the possible increased risks when prescribing parecoxib for patients at high risk of cardiovascular adverse events.

Parecoxib is not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of its lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including parecoxib.

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, exfoliative dermatitis and toxic epidermal necrolysis have 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 (see section 4.8). 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 in the first two weeks of treatment. DYNASTAT Injection 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.

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

Anaphylactoid Reactions

Anaphylactoid reactions were not reported in patients receiving DYNASTAT Injection in clinical trials. However, as with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to DYNASTAT Injection. DYNASTAT Injection should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see section 4.3 and section 4.4, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Hypersensitivity reactions (anaphylactic reactions and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib (see section 4.8). These reactions have occurred in patients with and without a history of allergic-type reactions to sulfonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

DYNASTAT Injection may Mask Fever

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.

In addition, caution should be exercised with respect to monitoring the incision for signs of infection in patients receiving DYNASTAT Injection. When used in post-CABG patients at a dose of 80 mg/day over 14 days, no increase in overall infection rate was seen. However, sternal wound infections occurred at a somewhat higher rate in patients receiving DYNASTAT compared to placebo (DYNASTAT 2.6%, placebo 2.0%, p=NS).

In the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) 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.

Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation

It is unclear, at the present time, how the rates of serious GI toxicity associated with NSAIDs that inhibit both COX-1 and COX-2, apply to DYNASTAT Injection. DYNASTAT Injection, a COX-2 specific inhibitor, does not affect COX-1 function as demonstrated by relevant clinical results.

Serious GI toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs), including DYNASTAT Injection. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

The ulcerogenic effects of DYNASTAT Injection and oral valdecoxib on the upper GI tract were examined in short-term (7 day) studies in young and elderly healthy subjects, and a 12-week study in OA patients, respectively. Significantly fewer endoscopically detected ulcers were seen with DYNASTAT Injection compared to ketorolac and naproxen, and with valdecoxib compared to ibuprofen and naproxen (see section 5.1).

Patients most at risk of developing GI complications with NSAIDs are elderly patients; patients with cardiovascular disease; patients using concomitant aspirin (even at low doses), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), other antiplatelet drugs, or other NSAIDs; patients ingesting alcohol; and patients with a history of, or active, GI disease (such as ulceration, bleeding, or inflammatory conditions). In addition, pharmacoepidemiological studies have identified several other co-therapies or co-morbid

conditions that may increase the risk for GI bleeding such as: treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, and poor general health status. DYNASTAT Injection should be prescribed with caution in these patients. Physicians and patients should remain alert for ulceration and bleeding even in the absence of symptoms.

Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimise the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered. Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors.

Hepatic Effects

Borderline elevations of one or more liver function tests were observed in 3.4% of surgical patients receiving DYNASTAT Injection and 5.8% of placebo patients. Notable elevations (greater than three or more times the Upper Limit of Normal) were seen in 0.7% of patients treated with DYNASTAT Injection and 0.8% of placebo patients.

Rare cases of severe hepatic reactions, including jaundice, fatal fulminant hepatitis, liver necrosis, hepatic failure (some with fatal outcome), and liver transplant have been reported with NSAIDs. In post-marketing experience, rare cases of jaundice, hepatomegaly, and hepatic failure have been reported with DYNASTAT Injection (see section 4.8).

A patient with symptoms and/or signs suggesting hepatic dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a hepatic reaction while on therapy with DYNASTAT Injection. If clinical signs and symptoms consistent with hepatic disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), DYNASTAT Injection should be discontinued.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in renal prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors, or angiotensin receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state. Clinical trials with valdecoxib have shown renal effects similar to those observed with comparator NSAIDs.

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

Caution is also recommended in patients with pre-existing renal disease. Even though, pharmacokinetically, there was no difference in excretion, in patients with severe renal

disease treatment with DYNASTAT Injection should be initiated with caution. Close monitoring of the patient's renal function is advisable.

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib (see section 4.8).

Concomitant Use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of medicine. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment (see section 4.5, Anti-hypertensives including ACE-inhibitors, Angiotensin Receptor Antagonists, Beta Blockers and Diuretics).

Concomitant Use of Oral Anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding (see section 4.5, Anticoagulants). Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

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.

Severe Hypotension

Cases of severe hypotension shortly following parecoxib administration have been reported in postmarketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The practitioner should be prepared to treat severe hypotension.

Fluid Retention and Oedema

Fluid retention and oedema have been observed in <1.0% of patients undergoing general surgery who received DYNASTAT Injection, similar to placebo. As with all NSAIDs, parecoxib may exacerbate pre-existing hypertension, cardiac failure or oedema, and the treatment of these conditions may be compromised. DYNASTAT Injection 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 hypovolaemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, DYNASTAT should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma (see section 4.3 and section 4.4, Anaphylactoid Reactions).

Paediatric Use

Safety and effectiveness in paediatric patients below the age of 18 have not been evaluated.

Use in the Elderly

Of the total number of patients who received DYNASTAT Injection in clinical trials, more than 250 were 65-74 years of age, while approximately 70 additional patients were 75 years and over. No overall differences in safety and effectiveness between these patients and younger patients have been identified, but greater sensitivity of some older individuals cannot be ruled out.

Effects on Laboratory Tests

Isolated laboratory abnormalities following surgery were seen in patients taking DYNASTAT Injection, placebo and comparators. No particular testing, other than appropriate post-operative laboratory monitoring, is indicated in patients receiving DYNASTAT Injection.

4.5 Interaction with other medicines and other forms of interaction

General

In vitro studies with human hepatic microsomal systems showed no significant inhibitory effects on CYP3A4, 2D6, 2E1, and 1A2 isoforms by parecoxib and valdecoxib. Weak inhibitory activity was found for 2C9 and 2C19 isozymes.

In humans, studies have demonstrated that valdecoxib metabolism is predominantly mediated via CYP450 3A4 and 2C9 isozymes. Glucuronidation is a further route of metabolism. Due to CYP450-mediated and non-CYP450-mediated metabolic pathways, genetic polymorphisms leading to substantially higher drug plasma concentrations resulting from impaired metabolism are not expected.

Aspirin

DYNASTAT Injection had no effect on aspirin-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that DYNASTAT Injection can be given with low dose aspirin. Because of its lack of platelet effects, DYNASTAT Injection is not a substitute for aspirin for cardiovascular prophylaxis.

Methotrexate

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate (5-20 mg IM), valdecoxib (10 mg BD and 40 mg BD) did not have a clinically significant effect on the plasma exposure to methotrexate. However, caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate.

Anti-hypertensives including ACE-inhibitors, Angiotensin Receptor Antagonists, Beta Blockers and Diuretics

Reports suggest that NSAIDs may diminish the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, beta blockers and diuretics. It is unclear, at the present time, how this may apply to DYNASTAT Injection. This potential interaction should be given consideration in patients taking DYNASTAT Injection concomitantly with ACE-inhibitors, angiotensin receptor 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 receptor 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.

Ciclosporin

Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with ciclosporin.

Injectable Anaesthetics

Propofol is metabolised by CYP2C9. Coadministration of parecoxib sodium with propofol did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics of IV propofol.

Midazolam is metabolised primarily by CYP3A4. Coadministration of parecoxib sodium IV, or valdecoxib orally, with IV midazolam did not affect the pharmacokinetics (metabolism and exposure) or the pharmacodynamics of midazolam.

Fentanyl and Alfentanil are extensively metabolised by CYP3A4. Coadministration with parecoxib sodium had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil.

Inhalation Anaesthetics

No formal interaction studies have been conducted. In the general surgery studies, no evidence of pharmacodynamic medicine interaction was observed between parecoxib sodium administered preoperatively and the inhalation anaesthetic agents nitrous oxide and isoflurane.

Glibenclamide

Glibenclamide is a CYP3A4 substrate. Coadministration of valdecoxib (10 mg BD for 7 days) with glibenclamide (5 mg or 10 mg OD) did not affect the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

Anticonvulsants

No clinically important interaction was seen with valdecoxib and phenytoin.

Potential interactions with carbamazepine (3A4 substrate) have not been studied. However, as mentioned above (see section 4.5, General), no interactions were noted using prototype 3A4 substrates of this isozyme.

Ketoconazole and Fluconazole

AUC and C_{max} of valdecoxib was increased (62%) when coadministered with fluconazole, indicating that the dose of parecoxib sodium should be reduced in those patients who are receiving fluconazole therapy. AUC and C_{max} of valdecoxib was increased (38%) when coadministered with ketoconazole.

Dextromethorphan

Valdecoxib 40 mg BD for 7 days did not produce clinically relevant inhibition in the metabolism by the CYP 2D6-mediated pathway involved in the conversion of dextromethorphan to dextrorphan.

Lithium

Valdecoxib 40 mg BD for 7 days produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentrations should be monitored closely when initiating or changing parecoxib sodium therapy in patients receiving lithium.

Anticoagulants

The effect of valdecoxib on the anticoagulant effect of warfarin (1 – 8 mg/day) was studied in healthy subjects by IV coadministration of 10 mg parecoxib sodium BD for 7 days. There was a slight increase in the plasma concentration of R-warfarin, but not S-warfarin, as a result of parecoxib sodium coadministration. The effect of oral valdecoxib (40 mg BD) on the anticoagulant effect of warfarin (1 – 8 mg/day) was studied in healthy subjects by coadminstration for 7 days. Valdecoxib caused a statistically significant increase in plasma exposure of R-warfarin and S-warfarin (12% and 15% respectively), and in the pharmacodynamic effects (prothrombin time, measured as INR of warfarin). While mean INR values were only slightly increased (≤8%) with coadministration of valdecoxib, the day-to-day variability in individual INR values was increased.

Anticoagulant therapy should be monitored, particularly during the first few days, after initiating DYNASTAT Injection therapy in patients receiving warfarin or similar agents, since these patients are at increased risk of bleeding complications.

Other

An interaction study was conducted between parecoxib and heparin. Interaction studies were also conducted between valdecoxib and oral contraceptives (ethinyloestradiol/norethisterone), omeprazole and diazepam. No clinically important interactions were seen in these studies.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category C

Teratogenic Effects

Embryo-fetal development studies conducted with intravenous parecoxib sodium in rats and rabbits have not shown any evidence of developmental malformations. Doses used (respectively up to 25 and 40 mg/kg/day) resulted in systemic exposures (plasma AUC) to valdecoxib that were 4.3-fold and 2.2-fold human exposure at the maximum recommended therapeutic dose, respectively. Animal reproduction studies are not always predictive of human responses, and there are no adequate and well-controlled studies in pregnant women. Use of DYNASTAT Injection during pregnancy is not recommended.

Non-Teratogenic Effects

Parecoxib sodium increased post-implantation losses in rats and rabbits at doses that resulted in systemic exposures (plasma AUC) to valdecoxib that were similar to the human exposure at the maximum recommended therapeutic dose. This effect is thought to be a consequence of the inhibition of prostaglandin synthesis, and has been reported to occur with other NSAIDs. No studies have been conducted to evaluate the effect of valdecoxib on the closure of the ductus arteriosus in humans or animals. The use of cyclooxygenase inhibitors may result in premature closure of the ductus arteriosus or uterine inertia. Therefore, the use of DYNASTAT Injection during the third trimester should be avoided.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. 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.

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. Pregnant women on parecoxib should be closely monitored for amniotic fluid volume.

Labour and Delivery

Parecoxib sodium has not been studied in late pregnancy and parturition in either animals or humans. In animal studies, both COX-1 and COX-2 have been shown to be present in the ductus arteriosus of fetal lambs and to contribute to the maintenance of patency and the fetal ductus arteriosus was constricted significantly in near-term rats.

Breast-feeding

Parecoxib, valdecoxib and an active metabolite of valdecoxib, are excreted in the milk of lactating rats. Parecoxib and valdecoxib are also reported to be transferred into the breast milk of lactating women. Because of the potential for adverse effects in nursing infants from DYNASTAT Injection, breast-feeding should be discontinued during treatment.

Fertility

Parecoxib sodium did not impair rat fertility at intravenous doses of 25 mg/kg/day (males) or 12.5 mg/kg/day (females). These doses resulted in systemic exposures (plasma AUC) that were 1.4-fold human exposure for valdecoxib, at the maximum recommended therapeutic dose (40 mg BD).

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, should be considered.

4.7 Effects on ability to drive and use machines

The effect of DYNASTAT Injection on ability to drive or use machinery has not been studied. However, patients who experience dizziness, vertigo or somnolence after receiving DYNASTAT Injection should refrain from driving or operating machinery.

4.8 Undesirable effects

Clinical Trial Experience

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%

Blood and lymphatic system disorders: post-operative anaemia

Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, vomiting

General disorders and administration site conditions: oedema peripheral

Infections and infestations: alveolar osteitis (dry socket)

Metabolism and nutrition disorders: hypokalaemia

Nervous system disorders: dizziness, hypoaesthesia

Psychiatric disorders: insomnia

Renal and urinary disorders: oliguria

Respiratory, thoracic and mediastinal disorders: respiratory insufficiency

Skin and subcutaneous tissue disorders: sweating increased, pruritus

Vascular disorders: hypotension

Events occurring ≥0.5% and <1%

Blood and lymphatic system disorders: thrombocytopenia

Cardiac disorders: bradycardia

Gastrointestinal disorders: mouth dry, flatulence

Infections and infestations: pharyngitis

Musculoskeletal and connective tissue disorders: back pain

Skin and subcutaneous tissue disorders: rash

Vascular disorders: hypertension

Events occurring <0.5%

Cardiac disorders: myocardial infarction

Ear and labyrinth disorders: earache

Gastrointestinal disorders: oesophagitis, gastroesophageal reflux, hypoactive bowel sounds, pancreatitis, perioral swelling, gastroduodenal ulceration

General disorders and administration site conditions: injection site pain, injection site reaction, asthenia

Immune system disorders: anaphylactoid reaction

Infections and infestations: abnormal sternal serous wound drainage, wound infection

Injury, poisoning and procedural complications: skin post-operative complications

Investigations: BUN increased, creatine phosphokinase increased, creatinine increase, LDH increased, AST increased, ALT increased

Metabolism and nutrition disorders: anorexia, hyperglycaemia

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

Immediately following CABG surgery, patients administered DYNASTAT have a higher risk of adverse events, such as cardiovascular/thromboembolic events (e.g. myocardial infarction and cerebrovascular accident), renal dysfunction, deep surgical infections or sternal wound healing complications (see section 4.3).

Post-Marketing Experience

In post-marketing experience, the following rare, serious adverse events have been reported in association with the use of parecoxib:

Renal failure, acute renal failure, aseptic meningitis, congestive heart failure, circulatory collapse, erythema multiforme, hepatic failure, hepatomegaly, jaundice, Stevens-Johnson syndrome and hypersensitivity reactions including anaphylaxis and angioedema (see section 4.4).

In post-marketing experience, in addition to the severe cutaneous adverse reaction erythema multiforme and Stevens-Johnson syndrome, the following events have been reported in association with the use of valdecoxib and cannot be ruled out for DYNASTAT Injection:

Myocardial infarction (very rare), exfoliative dermatitis and toxic epidermal necrolysis (see section 4.4). The reported rate of serious skin events appears to be greater for valdecoxib as compared to other COX-2 selective inhibitors.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No symptoms of overdose have been observed with single IV doses of up to 200 mg of parecoxib sodium or oral doses up to 400 mg of valdecoxib in healthy subjects. Parecoxib sodium doses of 50 mg BD IV for 7 days did not result in any signs of toxicity.

Patients should be managed by symptomatic and supportive care following an overdose. There are no specific antidotes. Valdecoxib is not removed by haemodialysis. Forced diuresis or alkalinisation of urine may not be useful due to high protein binding of valdecoxib.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib ATC Code: M01AH

Pharmacodynamic Effects

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. In animal models, the analgesic activity of valdecoxib is not reversible by naloxone. Therefore, DYNASTAT Injection is not expected to exhibit the potential for dependence, sedation or respiratory depression seen with opioid analgesic agents.

When given at the recommended doses for management of acute pain, the onset of analgesia was 7–14 minutes and reached a peak effect within 2 hours. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 24 hours.

Clinical Efficacy and Safety

The analgesic efficacy and broad clinical utility of valdecoxib (delivered parenterally as the parecoxib sodium prodrug, DYNASTAT Injection) have been demonstrated in multiple clinical models of pain. The analgesic efficacy of DYNASTAT Injection was determined by various standard, primary and secondary measures, including absolute and differential pain relief scales and patient global evaluation. Comparisons were made to ketorolac (15 mg IV, 30 mg IV; 60 mg IM) and morphine (4 mg IV). Doses of parecoxib sodium are expressed in terms of parecoxib, not the sodium salt.

Analgesic response to DYNASTAT Injection was found to be independent of age, gender or severity of pain.

Management of Pain

The perioperative efficacy of DYNASTAT Injection was established in studies of oral, gynaecologic, orthopaedic, and coronary artery bypass graft (CABG) surgical pain.

Post-oral Surgery

In single-dose post-oral surgery (extraction of ≥2 third molar teeth with bone removal) pain studies, patients were randomised to receive parecoxib sodium (1 to 100 mg), placebo, or an active control. The effective analgesic dose range for DYNASTAT Injection was 20 to 40 mg. Doses higher than 40 mg provided no additional analgesic efficacy. Onset of analgesia, following a single 20 or 40 mg dose of DYNASTAT Injection, was 11-14 minutes; magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM (see Table 1 for a representative study). In addition, the median duration of analgesia for the 40 mg dose was 15-22 hours, providing statistically significantly superior sustained pain relief over the 20 mg dose and comparators.

Table 1

Primary Efficacy Parameters for Single Doses of Parecoxib Sodium and Comparators – Post-oral Surgery

Analgesia Parameters	Parecoxib				Ketorolac	Placebo
	20 mg IM	20 mg IV	40 mg IM	40 mg IV	60 mg IM	
Time to Onset[†]	00:13*	00:13*	00:13*	00:13*	00:12*	>24:00
Duration (Time to Rescue Medication)[†]	09:20*	07:03*	21:43*	15:39*	11:01*	01:03
12 hr. Total Pain Relief (TOTPAR12)[‡]	23.43*	22.65*	30.04*	28.38*	29.91*	5.31

[†]Median times are expressed in hr:min

[‡]TOTPAR12 = Time weighted sum of the pain relief scores over the first 12 hours post-dose

* Significant difference from placebo, $p<0.05$

Analgesic effectiveness of single and multiple doses of DYNASTAT Injection for post-surgical pain was evaluated in 819 patients following gynaecologic (abdominal hysterectomy) or orthopaedic (hip or knee joint replacement) surgery.

Post-gynaecologic Surgery

DYNASTAT Injection was evaluated in single and multiple dose regimens in women with moderate to severe pain following abdominal hysterectomy. Single doses of DYNASTAT Injection 20 and 40 mg IV were compared to placebo, morphine 4 mg IV, and ketorolac 30 mg IV. Onset of analgesia, following a single dose of 40 mg of DYNASTAT Injection, was 7-14 minutes and the magnitude of the analgesic effect was comparable to that of ketorolac (Table2). Overall, a single dose of DYNASTAT Injection 40 mg was more efficacious than DYNASTAT Injection 20 mg. In the multiple dose treatment phase of the second study, 40 mg BD/PRN was comparable to 20 mg QID/PRN and both dose regimens were similar in effectiveness to ketorolac 30 mg QID/PRN.

Table 2

Primary Efficacy Parameters for Single Doses of Parecoxib Sodium and Comparators – Post-gynecologic Surgery

Analgesia Parameters	**Parecoxib**		**Morphine**	**Ketorolac**	**Placebo**
Time to Onset[†]	**20 mg IV**	**40 mg IV**	**4 mg IV**	**30 mg IV**	
N93-019	00:23	00:14*	00:23*	00:10*	>24:00
N93-021	00:13	00:07*	00:06	00:09*	00:14
Duration (Time to Rescue Medication)[†]					
N93-019	06:10*	06:30*	02:36	06:00*	01:50
N93-021	06:05	06:20*	04:55	06:10*	02:50
12 Hr. Total Pain Relief (TOTPAR12)[‡]					
N93-019	17.78*	17.35*	6.80	16.76*	4.89
N93-021	19.99*	26.44*	18.97*	25.32*	13.19

[†]Median times are expressed in hr:min

[‡]TOTPAR12 = Time weighted sum of the pain relief scores over the first 12 hours post-dose

* Significant difference from placebo, $p<0.05$

Post-orthopaedic Surgery

Two double-blind, parallel group studies were conducted in adults with moderate to severe pain following knee or hip replacement surgery. Both studies included a single-dose phase comparing DYNASTAT Injection 20 and 40 mg IV to placebo, morphine 4 mg IV and ketorolac 30 mg IV (knee replacement study) or ketorolac 15 mg IV (hip replacement study). Onset of analgesia, following a single dose of 40 mg of DYNASTAT Injection, was 10-11 minutes (Table 3). Overall, a single dose of DYNASTAT Injection 40 mg was more efficacious than 20 mg. In the hip replacement study, 20 mg QID/PRN was comparable to 40 mg BD/PRN, and both dose regimens were similar in effectiveness to ketorolac 15 mg IV, QID/PRN.

Table 3

Primary Efficacy Parameters for Single Doses of Parecoxib Sodium and Comparators – Post-orthopedic Surgery

Analgesia Parameters	Parecoxib		Morphine	Ketorolac	Placebo
Time to Onset†	20 mg IV	40 mg IV	4 mg IV	15 or 30 mg IV	
N93-018 (knee)	00:27	00:11	00:15	00:12*	00:31
N93-020 (hip)	00:12*	00:10*	00:10	00:15*	00:30
Duration (Time to Rescue Medication)†					
N93-018 (knee)	03:09*	05:10*	02:07	04:35*	01:48
N93-020 (hip)	06:53*	07:48*	03:20	06:14*	03:01
12 Hr. Total Pain Relief (TOTPAR12)‡					
N93-018 (knee)	13.17	17.95*	10.11	12.88*	8.26
N93-020 (hip)	22.58*	26.63*	13.48	16.52*	9.65

†Median times are expressed in hr:min

‡TOTPAR12 = Time weighted sum of the pain relief scores over the first 12 hours post-dose

* Significant difference from placebo, p<0.05

Patients who required any rescue medication in the gynaecologic and orthopaedic efficacy trials were withdrawn from the study (Table 4). As a result, experience is limited with parecoxib treatment for more than 2 days.

Table 4 Percent of Patients Withdrawn for Use of Rescue Medication

	Study 020	Study 021
Placebo	75% (27/36)	73% (32/44)
Parecoxib 20 mg	35% (15/43) * +	37% (14/38) *
Parecoxib 40 mg	39% (17/44) * +	41% (17/41) *

* difference statistically significant from placebo (p<0.01)

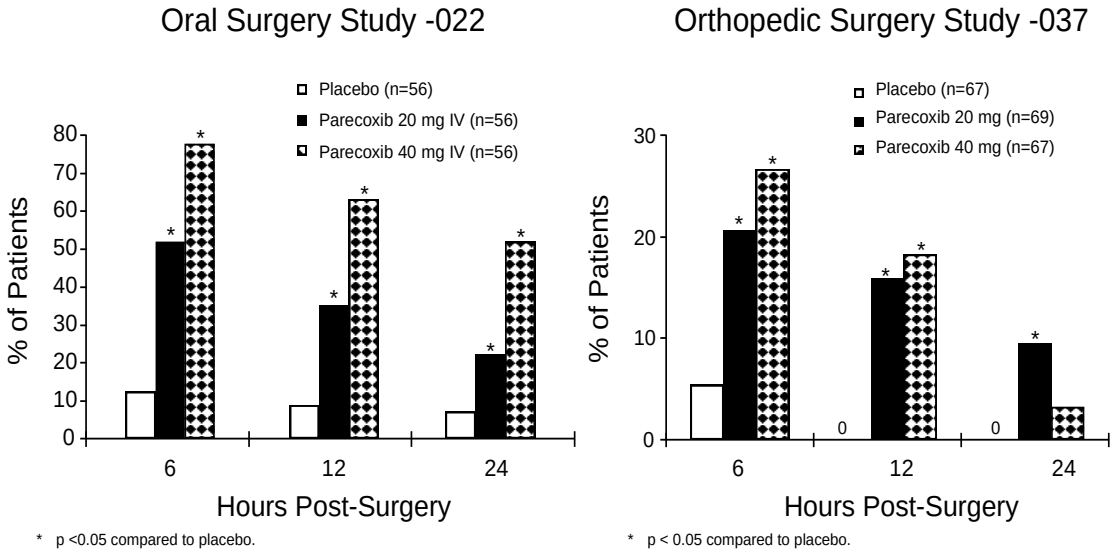
+ difference statistically significant from morphine (p<0.05)

Pre-operative Administration

Two clinical studies evaluating the pre-operative administration (i.e., pre-emptive dosing) of DYNASTAT Injection have demonstrated efficacy in reducing post-operative pain. Compared to placebo, administration of single doses of DYNASTAT Injection 30 to 45 minutes prior to surgery significantly delayed development of post-operative pain (as measured by the proportion of patients not requiring supplemental pain medication at 6, 12 and 24 hours post-surgery) in patients undergoing oral surgery, and orthopaedic (bunionectomy and total hip arthroplasty) surgery (Figure 1). The safety profile of DYNASTAT Injection administered pre-operatively was not different from that seen with post-operative administration.

Figure 1

Proportion of Patients Not Requiring Supplemental Pain Medication – Pre-operative Administration Studies



Special Studies

Gastrointestinal

Endoscopy studies were conducted to evaluate the ulcerogenic effects of DYNASTAT Injection on the upper gastrointestinal (GI) mucosa. In short-term (7 day) studies involving healthy young or elderly subjects (≥65 years), DYNASTAT Injection treatment resulted in significantly fewer ulcers than either ketorolac or naproxen (Table 5).

Table 5
Incidence (95% CL) of Endoscopic, Gastroduodenal Ulcers in Healthy Subjects

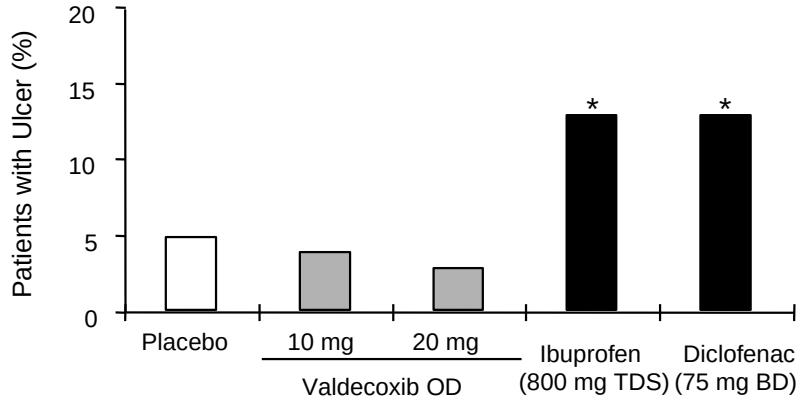
	Young Subjects		Elderly Subjects
	Study 1 n=166	Study 2 n=123	Study 3 n=94
Placebo	0%	0%	0%
Parecoxib sodium 20 mg BD	2% (6.2%)	--	--
Parecoxib sodium 40 mg BD	--	0%	0%
Ketorolac 15 mg QID	--	--	23%* (37.8%)
Ketorolac 30 mg QID	39%* (53.9%)	28%* (41.9%*)	--
Naproxen 500 mg BD	17%* (28.5%)	--	--
*p < 0.05 vs Parecoxib sodium and placebo in same study Parecoxib sodium not different from placebo in any study			

In a 12-week placebo-controlled study, scheduled endoscopies were conducted in 1150 patients with osteoarthritis. The gastroduodenal ulcer incidence rates with oral valdecoxib (active moiety of DYNASTAT Injection), diclofenac sodium, and ibuprofen were compared (Figure 2). Valdecoxib was associated with a statistically significantly lower incidence of endoscopic ulcers compared to ibuprofen and diclofenac over the study period.

There was no difference in the incidence of ulcers between placebo and either of the two doses of valdecoxib.

Figure 2

Incidence (%) of Gastroduodenal Ulcers Over 3 months in OA Patients



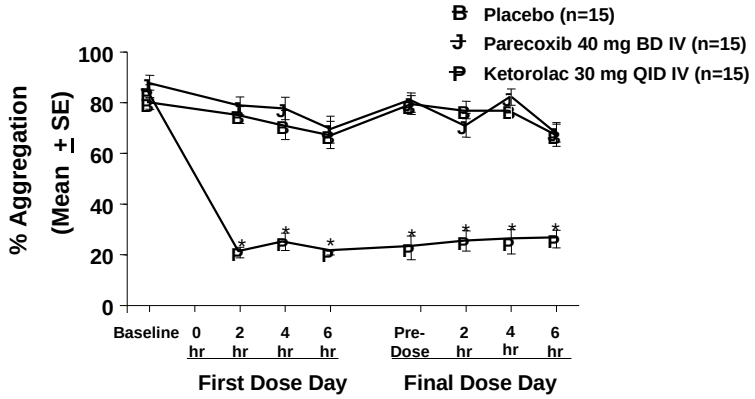
* Significant difference from placebo; p=0.010

Platelets

In clinical trials studying young and elderly (≥65 years) adult subjects, single and multiple doses up to 7 days of DYNASTAT Injection 20 mg and 40 mg BD, 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 (Figure 3). Full therapeutic doses of DYNASTAT Injection had no clinically significant effect on aspirin-mediated inhibition of platelet function compared to placebo (see section 4.5, Aspirin).

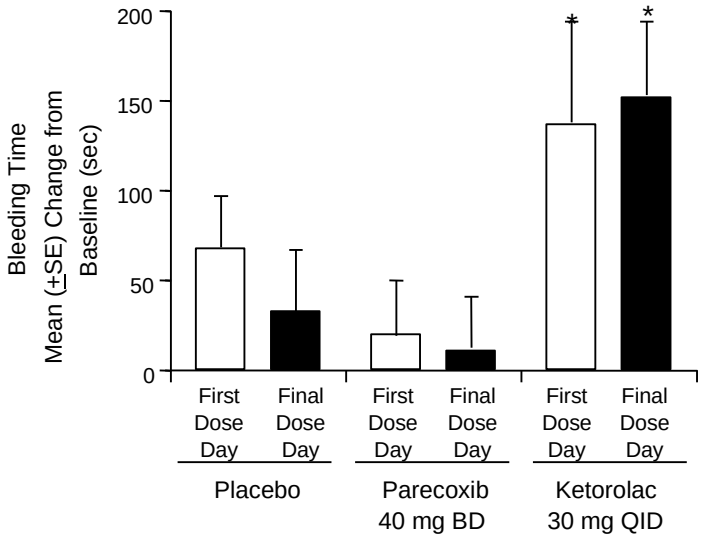
Figure 3

Platelet Aggregation Response to Arachidonate



*** *P* < 0.05 vs placebo and parecoxib**

Bleeding Time†



* p < 0.05 vs. placebo and parecoxib sodium.
† Mean (±SE) of bleeding time determination at 2, 4 and 6 hours on each dose day.

Post-operative Safety Studies (Two CABG Surgery and one General Surgery)

In addition to routine adverse event reporting, pre-specified event categories, adjudicated by an independent expert committee, were examined in three 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 10-14 days. All patients received standard of care analgesia during treatment. In the three studies, the overall adverse event profiles were similar between active treatments and placebo.

<u>CABG Surgery</u>

Patients received low-dose acetylsalicylic acid prior to randomisation and throughout the two CABG surgery studies. Patients at greater risk of a pre-specified event in the CABG surgery studies were older than 65 years, or with a history of peripheral vascular or cerebrovascular disease, or with poor post-surgical renal function. Pre-specified events that occurred with the highest incidence in the CABG surgery population involved the category of surgical wound complications, including deep surgical infections and sternal wound healing events.

The first CABG surgery study evaluated parecoxib sodium, followed by treatment with oral valdecoxib 40 mg bid in a 14-day, double-blind, parallel-group study. A potential for increased risk of cerebrovascular accidents and surgical wound complications (most involving the sternal wound) was observed with parecoxib sodium/valdecoxib treatment (n=311) compared with placebo treatment (n=151); however, statistically significant treatment differences were not detected for these or any other pre-specified event categories.

In the second CABG surgery study, which evaluated parecoxib sodium/valdecoxib 20 mg bid or placebo/valdecoxib 20 mg bid or placebo/placebo for 10 days, a greater incidence (p=0.033) of cardiovascular/thromboembolic events was observed with parecoxib sodium/valdecoxib treatment (2.0%; n=544), but not with placebo/valdecoxib treatment (1.1%; n=544), when compared to placebo/placebo treatment (0.5%; n=548). 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).

General Surgery

In the third study in major general surgery (N=1050), no significant differences in the overall safety profile, including the same pre-specified event categories used for the second CABG study described above, were observed with parecoxib sodium/valdecoxib 20 mg bid as compared to placebo treatment.

Cardiovascular Safety

A minimum of 3 days treatment with parecoxib and subsequent use of valdecoxib, the active metabolite of parecoxib, for a total duration of 10-14 days has been associated with an increased incidence of cardiovascular adverse events in patients undergoing coronary artery bypass surgery in two separate clinical trials.

In an analysis of non-cardiac controlled trials in which the majority of patients were treated for 2 days, patients treated with parecoxib 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 was powered to detect a doubling in the background rate of cardiovascular adverse events in patients treated with parecoxib.

5.2 Pharmacokinetic properties

The pharmacokinetics of the prodrug parecoxib sodium and its active moiety valdecoxib, have been evaluated in more than 1600 individuals, including patients with acute pain, hepatic disease, renal disease, and young and elderly healthy subjects.

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 (C_{max})] of valdecoxib following injection of parecoxib sodium is approximately linear in the dosage range of 1 mg to 100 mg IV and 1 mg to 40 mg IM given as a single dose, or 5 to 50 mg IV and 5 to 20 mg IM given repeatedly twice a day (BD). Steady state was reached within 4 days with BD dosing.

The pharmacokinetics of parecoxib and valdecoxib following single IV and IM doses of parecoxib sodium are shown in Table 6.

Table 6

Summary of Single Dose Disposition Kinetics of Parecoxib in Healthy Subjects

Mean (%CV) PK Parameter Values for Parecoxib					
Route	Dose (mg)	C_{max}, (ng/mL)	T_{max}, hr	Effective T½, hr	AUC (lqc) (hr*ng/mL)
IV	20	4679 (35)	0.036 (65)	0.381 (8)	699 (22)
IM	20	1255 (36)	0.217 (22)	0.340 (23)	663 (23)
Mean (%CV) PK Parameter Values for Valdecoxib					
Route	Dose (mg)	C_{max}, (ng/mL)	T_{max}, hr	Effective T½, hr	AUC (lqc) (hr*ng/mL)
IV	20	384 (28)	0.542 (42)	6.81 (22)	2358 (33)
IM	20	377 (37)	0.890 (18)	6.56 (22)	2383 (32)

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. Valdecoxib, but not parecoxib, is extensively partitioned into erythrocytes with an RBC to plasma concentration ratio of about 4:1 and a blood to plasma ratio of about 2.5:1. This ratio remains approximately constant with time and therapeutic blood concentrations, and therefore measurement of plasma concentrations of valdecoxib in pharmacokinetics studies is appropriate.

Biotransformation

Parecoxib is rapidly and almost completely converted to valdecoxib *in vivo* with a plasma half-life of <60 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.

Elimination

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 ($T_{1/2}$) of valdecoxib after IV or IM dosing of parecoxib sodium is about 8 hours. Plasma clearance (CL_p) for valdecoxib is about 6 L/hr. In patients undergoing haemodialysis the CL_p of valdecoxib was similar to the CL_p found in healthy subjects.

Special Populations

Elderly (>65 years)

DYNASTAT Injection has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. Valdecoxib steady state plasma exposures in elderly female subjects, when adjusted for body weight, are about 40% higher than those in young male subjects. Dose adjustment in the elderly is not generally necessary; however for elderly female patients weighing <50 kg, initiate treatment with half the usual recommended dose of DYNASTAT Injection (see section 4.2).

Children and Adolescents

DYNASTAT 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

Valdecoxib pharmacokinetics has been studied in patients with varying degrees of renal impairment. 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 renal dialysis (see section 4.2).

Hepatic Impairment

In patients with moderate (Child-Pugh score 7-9) hepatic impairment, treatment should be initiated with half the usual recommended dose of DYNASTAT Injection since valdecoxib exposures were more than doubled (130%) in these patients. However, moderate hepatic impairment did not result in reduced rate or extent of parecoxib conversion to valdecoxib. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10); therefore, the use of DYNASTAT Injection is contraindicated in these patients (see sections 4.2 and 4.3).

5.3 Preclinical safety data

Carcinogenicity

Long-term animal studies to evaluate the carcinogenic potential of parecoxib sodium have not been conducted.

Genotoxicity

Parecoxib sodium was not mutagenic in bacterial cells and the Hpoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) mutation assay in Chinese hamster ovary (CHO) cells. Parecoxib increased the incidence of chromosomal aberrations in an *in vitro* CHO cell assay, however, it was negative in an *in vivo* micronucleus and chromosomal aberration test in rat bone marrow. Valdecoxib was negative in assays for gene mutations and clastogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Dibasic sodium phosphate
Phosphoric acid and/or sodium hydroxide.

Diluent (where supplied):

Sodium chloride
Hydrochloric acid and/or sodium hydroxide
Water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

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 section 6.6, is **not** recommended as this may cause precipitation from solution.

6.3 Shelf life

Unreconstituted powder: 36 months from date of manufacture.

Sodium chloride solution (0.9% w/v) diluent (where supplied): 60 months from date of manufacture.

Reconstituted solution: 24 hours (not refrigerated). The reconstituted product should not be stored in a refrigerator or freezer.

6.4 Special precautions for storage

Store below 25ºC. Protect from light.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Parecoxib Sodium Vials

Glass vial with a sterilised, lyophilising, laminated stopper or rubber stopper; sealed with a flip-off cap on the aluminium overseal.

Diluent Ampoules (where supplied)

2 mL ampoule: Colourless, neutral glass.

DYNASTAT Powder for Injection

Supplied in packs of 10 sterile, single-use vials containing 40 mg parecoxib (as parecoxib sodium).

DYNASTAT Powder for Injection with Diluent for Injection

Supplied in packs of 1, 3 and 5 sterile, single-use vials, containing 40 mg parecoxib (as parecoxib sodium) and 2 mL ampoules with a fill volume of 2 mL sodium chloride solution (0.9% w/v).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitute DYNASTAT 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.

After reconstitution, DYNASTAT 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, DYNASTAT 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 section 6.2).

This product contains no antimicrobial agent. DYNASTAT 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.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand.

Toll free number: 0800 736 363

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 13 February 2003.

10. DATE OF REVISION OF THE TEXT

12 February 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Editorial change
4.4	To add DRESS syndrome