PT. Pfizer Indonesia
Local Product Document

Generic Name: Parecoxib
Trade Name: **DYNASTAT**
CDS Effective Date: May 26, 2023
Supersedes: February 17, 2022

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Elderly patients and patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).

- DYNASTAT is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

Asthma and Skin Reaction

DYNASTAT is contraindicated to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (see **WARNINGS** and **PRECAUTIONS**).

Congestive Heart Failure and Edema

DYNASTAT should be used with caution in patients with fluid retention or heart failure (see **WARNINGS**).

Hepatic Effects

Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with DYNASTAT (see **PRECAUTIONS**).

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 (see **WARNINGS**).

NAME OF THE MEDICINAL PRODUCT

DYNASTAT 40 mg powder and solvent for solution for injection.

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

THERAPEUTIC INDICATION

Short-term treatment of post-operative pain.

POSOLOGY AND METHOD OF ADMINISTRATION

Carefully consider the potential benefits and risks of DYNASTAT and other treatment option before deciding to use DYNASTAT. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. 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.

Parecoxib may be administered as single or multiple IV or IM doses on a regular or as needed schedule. After initiation of therapy, dosage should be adjusted based on patient response. Clinical studies with parecoxib were conducted using up to 7 days of treatment. Parecoxib is only indicated for patients with a need for parenteral therapy and for whom a similar benefit could not be obtained from alternative oral therapy. It is recommended that patients be transitioned to alternative oral therapy as soon as clinically indicated.

As the cardiovascular (CV) risk of cyclooxygenase-2 (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. However, the relevance of these findings for the short-term use of parecoxib in the post-operative setting has not been evaluated.

Elderly: No dosage adjustment is generally necessary in elderly patients (≥65 years). However, for elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of DYNASTAT and reduce the maximum daily dose to 40 mg.

Hepatic impairment: No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh scale 5-6). Introduce DYNASTAT with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh scale 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh scale >9); therefore, its use is not recommended in these patients.

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 renal impairment or patients who may be pre-disposed to fluid retention (see **WARNINGS** and **Pharmacokinetic Properties**).

Children and adolescents: DYNASTAT has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients (dibasic sodium phosphate heptahydrate, phosphoric acid, sodium hydroxide, sodium chloride, and hydrochloric acid).
- History of hypersensitivity to sulphonamides.
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs or other cyclooxygenase-2 (COX-2) selective inhibitors. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS** - Anaphylactoid Reaction, and **PRECAUTIONS** - Pre-existing Asthma).
- The third trimester of pregnancy and breast-feeding.
- Severe hepatic impairment (Child-Pugh >9).
- Active peptic ulceration or gastrointestinal bleeding.
- Inflammatory bowel disease.
- Severe congestive heart failure.
- Parecoxib is contraindicated for the treatment of post-operative pain immediately following coronary artery bypass graft (CABG) surgery and should not be used in this setting.

WARNINGS

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 Thrombotic Events
Clinical trials of several COX-2 selective and non-selective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal.

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. 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 CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of acetyl salicylic acid mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of acetyl salicylic acid and an NSAID does increase the risk of serious GI events (see **WARNINGS**, Gastrointestinal (GI) Effect - Risk of GI Ulceration, Bleeding, and Perforation).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
NSAIDS, including DYNASTAT can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including DYNASTAT, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment with DYNASTAT and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including DYNASTAT. DYNASTAT should be used with caution in patients with compromised cardiac function, pre-existing edema, or other conditions pre-disposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation
NSAIDs, including DYNASTAT, can cause serious gastrointestinal events including, inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends with longer duration of use, 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.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Upper gastrointestinal (GI) perforations, ulcers, or bleeds have occurred in patients treated with parecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, or patients with a history of, or active GI diseases, such as ulceration, bleeding or inflammatory conditions; or patients using concomitant aspirin. Patient using NSAIDs with prior history of ulcer disease or gastrointestinal bleeding has 10-fold higher risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of corticosteroids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or anticoagulants, longer duration of NSAID therapy, smoking, patients ingesting alcohol, older age, and poor general health status, however, there are currently no specific parecoxib clinical data. 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 minimize the potential risk for an adverse GI event, in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

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 an NSAID may cause a dose-dependent reduction in 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 and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of DYNASTAT in patients with advanced renal disease. Therefore, treatment with DYNASTAT is not recommended in these patients with advanced renal disease. If DYNASTAT therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to DYNASTAT. DYNASTAT should not be given to patients with the acetyl salicylic acid 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 acetyl salicylic acid or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS** – Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

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

Skin Reactions
NSAIDs, including DYNASTAT, can cause serious skin adverse events, such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS), which can be fatal. 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. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
There are no studies in pregnant women.

Use of DYNASTAT during pregnancy is not recommended

In late pregnancy, as with other NSAIDs, DYNASTAT should be avoided because it may cause 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 **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.

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, should be considered.

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

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).

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

PRECAUTIONS

General

DYNASTAT cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of DYNASTAT in reducing (fever and) inflammation may diminish the utility of these diagnostic signs in detecting infectious complications of presumed non-infectious, painful conditions. The concomitant use of parecoxib with other non-specific NSAIDs should be avoided.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including DYNASTAT. These laboratory abnormalities may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

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

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including DYNASTAT. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including DYNASTAT, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetyl salicylic acid, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving DYNASTAT who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing Asthma
Patients with asthma may have acetyl salicylic acid-sensitive asthma. The use of acetyl salicylic acid in patients with acetyl salicylic acid-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between acetyl salicylic acid and other non-steroidal anti-inflammatory drugs has been reported in such acetyl salicylic acid-sensitive patients, DYNASTAT should not be administered to patients with this form of acetyl salicylic acid sensitivity and should be used with caution in patients with pre-existing asthma.

Information for Patients
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. DYNASTAT, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS**).

2. DYNASTAT, like other NSAIDs, can cause gastrointestinal discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS** — Gastrointestinal (GI) Effects – Risk of Gastrointestinal Ulceration, Bleeding, and Perforation).

3. DYNASTAT, like other NSAIDs, can cause serious skin side effects, such as exfoliative dermatitis, SJS, and TENS, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity, such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).

7. In late pregnancy, as with other NSAIDs, DYNASTAT should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests or renal tests persist or worsen, DYNASTAT should be discontinued.

Drug Interactions

Anti-hypertensives including ACE-inhibitors, angiotensin II antagonists, beta-blockers, and diuretics: Reports suggest that NSAIDs 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 taking 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, coadministration 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.

Acetyl salicylic acid: When DYNASTAT is administered with acetyl salicylic acid, its protein binding is reduced, although the clearance of free DYNASTAT is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of parecoxib and acetyl salicylic acid is not generally recommended because of the potential of increased adverse effects.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **PRECAUTIONS**, Renal Effects), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

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

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. A pharmacokinetic interaction study was conducted using valdecoxib and methotrexate and no clinically important interactions were seen. However, caution is advised when NSAIDs are administered concomitantly with methotrexate, because NSAID administration may result in increased plasma levels of methotrexate.

Warfarin: See **WARNINGS**.

Drug/Laboratory Test Interactions

Only if positive interactions have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Usually only if significant findings have been observed.

Pregnancy
Teratogenic effects: Pregnancy Category C
Reproductive studies conducted rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Non-teratogenic effects: Because of the known effects of non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and delivery: In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreases pup survival occurred. The effects of DYNASTAT on labor and delivery in pregnant women are unknown.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from 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.

Pediatric use
Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric use
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

Effects on ability to drive and use machines
No studies on the effect of DYNASTAT on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving DYNASTAT should refrain from driving or operating machines.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

DYNASTAT had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trial indicates that DYNASTAT can be given with low dose acetylsalicylic acid (≤325 mg).

Coadministration of parecoxib sodium and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors or diuretics are administered with parecoxib sodium.

Coadministration of NSAIDs and cyclosporine or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporine and tacrolimus. Renal function should be monitored when parecoxib sodium and any of these medicinal products are co-administered.

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. When DYNASTAT was co-administered with morphine, a smaller dose (by 28%-36%) of morphine could be used to achieve the same clinical level of analgesia.

Effects of the other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)
Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isoenzymes.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib sodium should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor); however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme indication has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers, such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effects of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products
Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering DYNASTAT and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g., flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CY2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering DYNASTAT with medicinal products known to be substrate of CYP2C19 (e.g., phenytoin, diazepam or imipramine).

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate intramuscularly, orally administered valdecoxib (40 mg twice daily) did not have a clinically significant effect on the plasma concentrations of methotrexate. However, adequate monitoring of methotrexate-related toxicity should be considered when co-administering these two medicinal products.

Coadministration of valdecoxib and lithium produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentration should be monitored closely when initiating or changing parecoxib sodium therapy in patients receiving lithium.

Coadministration of valdecoxib with glibenclamide (CYP3A4 substrate) did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

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

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

UNDESIRABLE EFFECTS

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%

Gastro-intestinal disorders: abdominal pain constipation, dyspepsia, vomiting.
General disorders and administration site conditions: edema peripheral.
Infections and infestations: alveolar osteitis (dry socket).
Nervous system disorders: hypoaesthesia, dizziness.
Psychiatric disorders: insomnia.
Red blood cell disorders: post-operative anaemia.
Skin and subcutaneous tissue disorders: sweating increased, pruritus.
Renal and urinary disorders: oliguria.
Vascular disorders: hypotension.

Events occurring ≥0.5% and <1%

Gastrointestinal disorders: mouth dry, flatulence, gastroduodenal ulceration.
Musculoskeletal and connective tissue disorders: back pain.
Cardiac disorders: bradycardia.
Liver and biliary system disorders: SGOT increased, SGPT increased.
Infections and infestations: pharyngitis, respiratory insufficiency.
Platelet, bleeding and clotting disorders: thrombocytopenia.
Skin 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, perioral swelling.
General disorders and administration site conditions: injection site pain, injection site reaction, asthenia, abnormal sternal serous wound drainage, wound infection.
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, hypokalaemia.
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.

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for DYNASTAT: acute renal failure, congestive heart failure, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered DYNASTAT may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication.

In post-marketing experience, the following reactions have been reported in association with the use of valdecoxib and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, erythema multiforme, acute renal failure, hypersensitivity reactions including anaphylaxis and angioedema (see **WARNINGS**), exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis.

Post-marketing Surveillance

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

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.

Overdose

No case of parecoxib overdose has been reported.

In case of acute overdose, patients should be managed by symptomatic and supportive care. There are no specific antidotes. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH.

Parecoxib is a prodrug of valdecoxib. The mechanism of action of valdecoxib is by inhibition of cyclooxygenase-2 (COX-2)-mediated prostaglandin synthesis. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2 have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. At therapeutic doses, valdecoxib is a COX-2 selective inhibitor of both peripheral and central prostaglandin and does not inhibit COX-1, thereby sparing COX-1 dependent physiological processes in tissues, particularly the stomach, intestine and platelets. COX-2 is also thought to be involved in ovulation, implantation and closure of the ductus arteriosus and central nervous system functions (fever induction, pain perception and cognitive function).

Clinical Studies

Parecoxib has been studied in a broad range of major and minor surgeries. The efficacy of DYNASTAT was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 to 13 minutes with clinically meaningful analgesia demonstrated in 23 to 29 minutes and a peak effect within 2 hours following administration of single dose of 40 mg IV or IM 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 randomised placebo-controlled trials, where the protocols allowed treatment of parecoxib for >3 days was pooled and analysed, 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, at recommended doses, significantly reduced opioid consumption and patient-reported opioid-related adverse effects (fatigue, drowsiness, confusion, inability to concentrate, dizziness, nausea, constipation, difficult urination, itching, retching/vomiting), while providing improved pain relief compared to opioids alone.

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

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

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 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 (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.

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

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

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

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

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

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

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 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.

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

CABG surgery study, for parecoxib sodium/valdecoxib compared to placebo treatment in these post-surgical patients.

Pharmacokinetic Properties

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

Absorption
Exposure of valdecoxib following single doses of 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 sodium 20 mg, C_{max} of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C_{max} following IV and IM administration. Exposure to parecoxib was similar after IV and IM administration in terms of AUC. Average C_{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C_{max} of valdecoxib is comparable after IM and IV parecoxib sodium administration.

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

Metabolism
Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid *in vivo* with a plasma half-life approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) of the sulphonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10% of the concentration of valdecoxib; because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium.

Elimination
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib recovered in the urine. No unchanged parecoxib is detected in urine and only trace amounts in the faeces. About 70% of the dose is excreted in the urine as inactive metabolites. Plasma clearance (CL_p) for valdecoxib is about 6 l/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life ($t_{½}$) of valdecoxib is about 8 hours.

Elderly Subjects: DYNASTAT has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. In healthy elderly subjects, the apparent oral clearance of

valdecoxib was reduced, resulting in an approximately 40% higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted for body weight, steady-state plasma exposure of valdecoxib was 16% higher in elderly females compared to elderly males.

Renal Impairment: In patients with varying degrees of renal impairment administered 20 mg IV DYNASTAT, parecoxib was rapidly cleared from plasma. Because renal elimination of valdecoxib is not important to its disposition, no changes in valdecoxib clearance were found even in patients with severe renal impairment or in patients undergoing dialysis.

Hepatic Impairment: Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh scale 7-9), treatment should be initiated with the usual recommended dose of DYNASTAT and the maximum daily dose should be reduced to 40 mg since valdecoxib exposures were more than doubled (130%) in these patients. Patients with severe hepatic impairment have not been studied and therefore, the use of DYNASTAT in patients with severe hepatic impairment is not recommended.

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.

Preclinical data reveal no special hazard for human based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib. However, in the repeated dose toxicity studies in dogs and rats, the systemic exposure 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.

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

These effects of parecoxib have not been evaluated in late pregnancy or in the pre- and post-natal period. Parecoxib sodium administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib-active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib sodium has not been evaluated.

INCOMPATIBILITIES

Following reconstitution with an acceptable diluent, parecoxib sodium may be injected into an IV line delivering 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Lactated Ringers Injection, or 5% Dextrose and 0.45% Sodium Chloride Injection. Injection into a line delivering 5% Dextrose in Lactated Ringer's, or other IV fluid not listed here, is not recommended, as this may cause precipitation from solution.

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

DYNASTAT and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 5% in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is not recommended.

Use of Sterile water for Injection is not recommended, as the resulting solution is not isotonic.

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

PRESENTATION

- DYNASTAT 40 mg: Each box contains 1 vial with parecoxib 40 mg and 1 ampoule with 2 ml sodium chloride 0.9% solution; Reg. No.: DKI0886101544A1

STORAGE AND CONDITION

Store below 30°C and keep container in the outer carton to protect from light. Do not refrigerate or freeze reconstituted solutions.

After reconstitution the products should be used immediately.

Keep out of the reach of children.

HARUS DENGAN RESEP DOKTER

DYNASTAT 40 mg
Manufactured by:
Pharmacia & Upjohn Company LLC, Kalamazoo, USA

Packed and released by:
Pfizer Manufacturing Belgium NV, Puurs, Belgium

Sodium Chloride Injection
Manufactured by:
Pfizer Manufacturing Belgium NV, Puurs, Belgium

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia