

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 20 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg vial: Each vial contains 20 mg parecoxib (present as 21.18 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4).

4.2 Posology and method of administration

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. (see section 6.6 for instructions for reconstitution)

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 (see section 5.2).

Hepatic Impairment: No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce Dynastat with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥ 10), therefore its use is contraindicated in these patients. (see sections 4.3 and 5.2)

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 predisposed to fluid retention. (see sections 4.4 and 5.2)

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

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Known hypersensitivity to sulphonamides (see sections 4.4 & 4.8).

Active peptic ulceration or gastrointestinal (GI) bleeding.

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score \geq 10).

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Treatment of post-operative pain following coronary artery bypass graft (CABG) surgery (see section 4.8 and 5.1).

Established ischaemic heart disease and/or cerebrovascular disease

4.4 Special warnings and special precautions for use

There is limited clinical experience with Dynastat treatment beyond three days.

Because of the possibility for increased adverse reactions at higher doses parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see section 4.2)

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with parecoxib sodium after careful consideration (see 5.1).

[Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients \(see section 5.1\). Dynastat has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft procedures.](#) Studies in other surgeries than CABG procedures included patients with ASA (American Society of Anaesthesiology) Physical Status Class I-III only.

COX-2 inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib sodium is taken concomitantly with acetylsalicylic acid (even at low doses).

Dynastat has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Serious skin reactions, some of them fatal, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib. These serious cutaneous reactions cannot be ruled out for parecoxib (the prodrug of valdecoxib) (see section 4.8). Patients appear to be at highest risk for these events early in the course of therapy; the onset of the event occurring in the majority of cases within the first 2 weeks of treatment.

Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. The reported rate of serious skin events appears to be greater for valdecoxib as compared to other COX-2 selective inhibitors. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see Section 4.3). Patients without a history of sulphonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib (see section 4.8). Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Dynastat in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Dynastat in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Dynastat.

Dynastat should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)

If during treatment, patients deteriorate with respect to any of the events described above, appropriate measures should be taken and discontinuation of parecoxib sodium therapy should be considered.

Dynastat may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Dynastat. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Dynastat.

Caution should be exercised when co-administering Dynastat with warfarin and other oral anticoagulants. (see section 4.5)

The use of Dynastat, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

4.5 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 other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed (see section 4.4).

Dynastat had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Dynastat can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see section 5.1).

Co-administration 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 co-administered with parecoxib sodium.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin 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. 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 other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib 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 induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering 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 (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Dynastat with medicinal products known to be substrates 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.

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

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

Injectable anaesthetics: Coadministration of IV parecoxib sodium 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib 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. (see section 5.1)

4.6 Pregnancy and lactation

Pregnancy:

The use of Dynastat is contraindicated in the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia. (see sections 4.3, 5.1 and 5.3)

Like other medicinal products that inhibit COX-2, Dynastat is not recommended in women attempting to conceive. (see sections 4.4, 5.1 and 5.3)

There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown. Dynastat should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

Parecoxib, valdecoxib (its active metabolite) and a valdecoxib active metabolite are excreted in the milk of rats. It is not known whether valdecoxib is excreted in human milk. Dynastat should not be administered to women who breast-feed. (see sections 4.3 and 5.3)

4.7 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.

4.8 Undesirable effects

Of the Dynastat treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Dynastat 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0 % for patients receiving Dynastat and 4.3% for patients receiving placebo.

[Very Common (>1/10), Common (\geq 1/100, <1/10) Uncommon (\geq 1/1000, <1/100) Rare (\geq 1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

Infections and infestations

Uncommon: abnormal sternal serous wound drainage, wound infection.

Blood and lymphatic system disorders

Common: post-operative anaemia

Uncommon: thrombocytopenia

Metabolism and nutrition disorders

Common: hypokalaemia

Psychiatric disorders:

Common: agitation, insomnia

Nervous system disorders

Common: hypoaesthesia

Uncommon: cerebrovascular disorder

Cardiac disorders

Uncommon: bradycardia

Vascular disorders

Common: hypertension, hypotension

Uncommon: aggravated hypertension

Respiratory, thoracic and mediastinal disorders

Common: pharyngitis, respiratory insufficiency

Gastrointestinal disorders

Common: alveolar osteitis (dry socket), dyspepsia, flatulence

Uncommon: gastroduodenal ulceration

Skin and subcutaneous tissue disorders

Common: pruritus

Uncommon: ecchymosis

Musculoskeletal and connective tissue disorders

Common: back pain

Renal and urinary disorders

Common: oliguria

General disorders and administration site conditions

Common: peripheral oedema

Investigations

Common: blood creatinine increased

Uncommon: SGOT increased, SGPT increased, blood urea nitrogen increased.

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: bronchospasm and hepatitis.

Following coronary artery bypass graft surgery, patients administered Dynastat have a higher risk of adverse events, such as cardiovascular/ thromboembolic events, deep surgical infections and sternal wound healing complications. Cardiovascular/thromboembolic events include myocardial infarction, stroke/TIA, pulmonary embolus and deep vein thrombosis (see section 4.3 and 5.1).

In post-marketing experience, the following rare, serious adverse events have been reported in association with the use of parecoxib: acute renal failure, congestive heart failure, erythema multiforme and hypersensitivity reactions including anaphylaxis and angioedema (see section 4.4).

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: myocardial infarction (very rare), exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).

4.9 Overdose

No case of parecoxib overdose has been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. 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. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

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 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses 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.

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%).

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 10-14 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 bid for a minimum of 3 days, followed by treatment with valdecoxib 40 mg bid (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 Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (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).

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 Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=525) for the remainder of a 10 day treatment period, or placebo IV followed by placebo PO (n=525). There were no significant differences in the overall safety profile, including the four pre-specified event categories described above for the second CABG surgery study, for parecoxib sodium/valdecoxib compared to placebo treatment in these post-surgical patients.

Platelet studies: In a series of small, multiple dose studies in healthy young and elderly subjects, Dynastat 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Dynastat 40 mg twice daily had no clinically significant effect on acetylsalicylic acid -mediated inhibition of platelet function. (see section 4.5)

5.2 Pharmacokinetic properties

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

Absorption

Exposure 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 or IM administration in terms of AUC. Average C_{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C_{max} of valdecoxib is comparable after IM and IV parecoxib sodium administration.

Distribution

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

Metabolism

Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (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 ($t_{1/2}$) 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. (see section 4.2)

Renal Impairment: In patients with varying degrees of renal impairment administered 20 mg IVDynastat, 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. (see section 4.2)

Hepatic Impairment: Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh score

7-9), treatment should be initiated with half the usual recommended dose of 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. (see sections 4.2 and 4.3)

5.3 Preclinical safety data

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

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.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Dibasic sodium phosphate, heptahydrate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

20 mg vial: When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.22 mEq of sodium per vial.

6.2 Incompatibilities

This medicinal product must **not** be mixed with other medicinal products other than those mentioned in 6.6.

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

Use of Ringer-Lactate solution for injection or glucose 50 g/l (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 Dynastat into an IV line delivering any other drug. The IV line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility (see section 6.6)

Injection into an IV line delivering glucose 50 g/l (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in 6.6, is **not** recommended as this may cause precipitation from solution.

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 12 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

6.5 Nature and contents of container

Parecoxib sodium vials

20 mg vials: Type I colourless glass vials (2 ml) with a laminated stopper, sealed with a yellow flip-off cap on the aluminium overseal.

Dynastat is available in packs containing 10 vials.

6.6 Instructions for use and handling <and disposal>

Dynastat must be reconstituted before use. Dynastat is preservative free. Aseptic technique is required for its preparation.

Reconstitution solvents

Acceptable solvents for reconstitution of Dynastat are:

sodium chloride 9 mg/ml (0.9%) solution

glucose 50 g/l (5%) solution for infusion

sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

Reconstitution process

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).

Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the 20 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 20 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, Dynastat should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter is observed. Dynastat should be administered within 24 hours of reconstitution (See Section 6.3), or discarded.

The reconstituted product is isotonic.

IV line solution compatibility

After reconstitution with acceptable solvents, Dynastat may **only** be injected IV or IM, or into IV lines delivering:

sodium chloride 9 mg/ml (0.9%) solution

glucose 50 g/l (5%) solution for infusion

sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
Ringer-Lactate solution for injection

For single use only. Any unused solution, solvent or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/001

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