ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg parecoxib (as 42.36 mg parecoxib sodium). After reconstitution, the concentration of parecoxib is 20 mg/ml. Each 2 ml of reconstituted powder contains 40 mg of parecoxib.

Excipient with known effect
This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.44 mmol of sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain in adults.

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

4.2 Posology and method of administration

Posology
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.

As the cardiovascular risk of 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. There is limited clinical experience with Dynastat treatment beyond three days (see section 5.1).

Concomitant use with opioid analgesics
Opioid analgesics can be used concurrently with parecoxib, dosing as described in the paragraph above. In all clinical assessments parecoxib was administered at a fixed time interval whereas the opioids were administered on as needed basis.

Elderly
No dose adjustment is generally necessary in elderly patients (≥65 years). However, for elderly patients weighing less than 50 kg, treatment should be initiated with half the usual recommended dose of Dynastat and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic impairment
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). No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Dynastat should be introduced with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and the maximum daily dose should be reduced to 40 mg.

Renal impairment
In patients with severe renal impairment (creatinine clearance <30 ml/min.) or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose (20 mg) and the patient's kidney function should be closely monitored (see sections 4.4 and 5.2). On the basis of pharmacokinetics, no dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min.).

Paediatric population
The safety and efficacy of parecoxib in children under 18 years old have not been established. No data are available. Therefore, parecoxib 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 medicinal product before administration, see section 6.6.

Precipitation may occur when Dynastat is combined in solution with other medicinal products and therefore Dynastat must not be mixed with any other medicinal product, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility.

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

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion;

or

- Ringer-Lactate solution for injection.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome), toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulfonamides (see sections 4.4 and 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 nonsteroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors.

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

Severe hepatic impairment (serum albumin <25 g/l or Child-Pugh score ≥10).

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

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

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Dynastat has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is limited experience in other types of surgery, for example gastrointestinal or urological surgery (see section 5.1).

Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.

Because of the possibility for increased adverse reactions at higher doses of 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). There is limited clinical experience with Dynastat treatment beyond three days (see section 5.1).

If, during treatment, patients deteriorate in any of the organ system functions described below, appropriate measures should be taken and discontinuation of parecoxib therapy should be considered.

Cardiovascular
COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with parecoxib after careful consideration (see section 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. Dynastat has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft (CABG) procedures. Studies in types of surgery other than CABG procedures included patients with American Society of Anaesthesiology (ASA) Physical Status Class I-III only.

Acetylsalicylic acid and other NSAIDs
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). Caution should be exercised when coadministering Dynastat with warfarin and other oral anticoagulants (see section 4.5). The concomitant use of parecoxib with other non- acetylsalicylic acid NSAIDs should be avoided.

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.

Gastrointestinal
Upper gastrointestinal (GI) 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, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding, or patients using acetylsalicylic acid concomitantly. The NSAIDs class is also associated with increased GI complications when coadministered with glucocorticoids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or patients ingesting alcohol. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Skin reactions
Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib. Additionally, fatal reports of toxic epidermal necrolysis have been reported through post-marketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib (see section 4.8). Some NSAIDs and selective COX- 2 inhibitors have been associated with an increased risk of generalized bullous fixed drug eruptions (GBFDE). 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 reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment.

Appropriate measures should be taken by physicians to monitor for any serious skin reactions with therapy, e.g. additional patient consultations. Patients should be advised to immediately report any emergent skin condition to their physician.

Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors. Patients with a history of sulfonamide allergy may be at greater risk of skin reactions (see section 4.3). Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity
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 sulfonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

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 physician should be prepared to treat severe hypotension.

Fluid retention, oedema, renal
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, preexisting oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken.

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.

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. 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. If blood pressure rises significantly, alternative treatment should be considered.

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

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) (see section 4.5).

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

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).

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

Inhibition of prostaglandins by NSAIDs, including COX-2 inhibitors, may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers and diuretics. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers and diuretics.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors or Angiotensin-II antagonists, may result in further 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.

Coadministration of NSAIDs and ciclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus because of NSAID effects on renal prostaglandins. Renal function should be monitored when parecoxib and any of these medicinal products are coadministered.

Dynastat may be coadministered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when coadministered with parecoxib.

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 coadministered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib 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 coadministered 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 coadministered 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 coadministering 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 two pharmacokinetic interaction studies in rheumatoid arthritis patients receiving a stable weekly methotrexate dose (5-20 mg/week, as a single oral or intramuscular dose), orally administered valdecoxib (10 mg twice daily or 40 mg twice daily) had little or no effect on the steady-state plasma concentrations of methotrexate. However caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate. Adequate monitoring of methotrexate-related toxicity should be considered when coadministering parecoxib and methotrexate.

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 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 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 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 was administered pre-operatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib and the inhalation anaesthetic agents nitrous oxide and isoflurane (see section 5.1).

4.6 Fertility, pregnancy, and lactation

Pregnancy
There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality (see sections 5.1 and 5.3). From the 20th week of pregnancy onward, Dynastat use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Dynastat should not be given unless clearly necessary. If Dynastat is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Dynastat for several days from gestational week 20 onward. Dynastat should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Dynastat is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding
Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into

human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Dynastat must not be administered to women who breast-feed (see section 4.3).

Fertility
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 4.3, 5.1 and 5.3).

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 Dynastat should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence after receiving Dynastat should refrain from driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reaction for Dynastat is nausea. The most serious reactions occur uncommonly to rarely, and include cardiovascular events such as myocardial infarction and severe hypotension, as well as hypersensitivity events such as anaphylaxis, angioedema, and severe skin reactions. Following coronary artery bypass graft surgery, patients administered Dynastat have a higher risk of adverse reactions such as: cardiovascular/thromboembolic events (including myocardial infarction, stroke/TIA, pulmonary embolus, and deep vein thrombosis; see sections 4.3 and 5.1), deep surgical infections, and sternal wound healing complications.

Tabulated list of adverse reactions
The following adverse reactions were reported for patients who received parecoxib (N=5,402) in 28 placebo-controlled clinical trials. Reports from post-marketing experience have been listed as "frequency not known" because the respective frequencies cannot be estimated from the available data. Within each frequency grouping, adverse reactions are listed using MedDRA terminology and presented in order of decreasing seriousness.

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Infections and infestations				
	Pharyngitis, alveolar osteitis (dry socket)	Abnormal sternal serous wound drainage, wound infection		
Blood and lymphatic system disorders				
	Anaemia postoperative	Thrombocytopenia		
Immune system disorders				
			Anaphylactoid reaction	
Metabolism and nutrition disorders				
	Hypokalaemia	Hyperglycaemia, anorexia		

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Psychiatric disorders				
	Agitation, insomnia			
Nervous system disorders				
	Hypoaesthesia, dizziness	Cerebrovascular disorder		
Ear and labyrinth disorders				
		Ear pain		
Cardiac disorders				
		Myocardial infarction, bradycardia		Circulatory collapse, congestive heart failure, tachycardia
Vascular disorders				
	Hypertension, hypotension	Hypertension (aggravated), orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders				
	Respiratory insufficiency	Pulmonary embolism		Dyspnoea
Gastrointestinal disorders				
Nausea	Abdominal pain, vomiting, constipation, dyspepsia, flatulence	Gastroduodenal ulceration, gastrooesophageal reflux disease, dry mouth, gastrointestinal sounds abnormal	Pancreatitis, oesophagitis, oedema mouth (perioral swelling)	
Skin and subcutaneous tissue disorders				
	Pruritus, hyperhidrosis	Ecchymosis, rash, urticaria		Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
Musculoskeletal and connective tissue disorders				
	Back pain	Arthralgia		
Renal and urinary disorders				
	Oliguria		Renal failure acute	Renal failure,
General disorders and administration site conditions				
	Oedema peripheral	Asthenia, injection site pain, injection site reaction		Hypersensitivity reactions including anaphylaxis and angioedema
Investigations				
	Blood creatinine increased	Blood CPK increased, blood LDH increased, SGOT increased, SGPT increased, BUN increased.		

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Injury, poisoning and procedural complications				
		Post procedural complication (skin)		

Description of selected adverse reactions
In post-marketing experience, toxic epidermal necrolysis has been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib (see section 4.4). In addition, the following rare, serious adverse reactions have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: bronchospasm and hepatitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, Coxibs, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective 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.

Parecoxib has been used in a 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 7-13 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.

Use of parecoxib beyond 3 days

Most trials were designed for dosing of parecoxib up to 3 days. Data from 3 randomised placebo-controlled trials, where the protocols allowed treatment of parecoxib for >3 days was pooled and analysed. In the pooled analysis of 676 patients, 318 received placebo and 358 received parecoxib. Of the patients treated with parecoxib, 317 patients received parecoxib for up to 4 days, 32 patients for up to 5 days, while only 8 patients were treated for up to 6 days and 1 patient for 7 or more days. Of the patients treated with placebo, 270 patients received placebo for up to 4 days, 43 patients for up to 5 days, while only 3 patients were treated for up to 6 days and 2 patients for 7 or more 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 4-7 days for parecoxib and 4-9 days for placebo. The occurrence of adverse events in patients receiving parecoxib for 4-7 days (median duration 4 days) was low after treatment Day 3 and similar to placebo.

Opioid-sparing effects

In a placebo-controlled, orthopedic, and general surgery study (n =1050), patients received Dynastat at an initial parenteral dose of 40 mg IV followed by 20 mg twice daily for a minimum of 72 hours in addition to receiving standard care including supplemental patient controlled opioids. The reduction in opioid use with Dynastat treatment on Days 2 and 3 was 7.2 mg and 2.8 mg (37% and 28% respectively). This reduction in opioid use was accompanied by significant reductions in patient-reported opioid symptom distress. Added pain relief compared to opioids alone was shown. Additional studies in other surgical settings provided similar observations. There are no data indicating less overall adverse events associated with the use of parecoxib compared to placebo when used in conjunction with opioids.

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

period (4.8% and 1.3% respectively). Surgical wound complications (most involving the sternal wound) were observed at an increased rate with parecoxib/valdecoxib treatment.

In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib 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/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 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 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.

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

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, the elimination half-life ($t_{1/2}$) of valdecoxib is about 8 hours.

Elderly
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 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 (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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib. 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 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 has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

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

Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is **not** recommended.

Use of water for injection is **not** recommended, as the resulting solution is not isotonic.

<u>After reconstitution</u>
Dynastat should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility (see section 6.6).

Injection of the reconstituted product into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in section 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

The shelf life of the unreconstituted product is 3 years.

Chemical and physical in-use stability of the reconstituted solution, which should not be refrigerated or frozen, have been demonstrated for up to 24 hours at 25°C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable products, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Type I colourless glass vials (5 ml) with a butyl rubber stopper, sealed with a purple polypropylene flip-off cap on the aluminium overseal.

Dynastat is available in packs containing 10 vials.

6.6 Special precautions for disposal and other handling

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

Reconstitution process
Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib).
Remove the purple flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, the liquid should be a clear solution. 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 for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion;

or

- Ringer-Lactate solution for injection.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2002
Date of latest renewal: 24 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder vial: Each vial contains 40 mg parecoxib (as 42.36 mg parecoxib sodium). After reconstitution, the concentration of parecoxib is 20 mg/ml. Each 2 ml of reconstituted powder contains 40 mg of parecoxib.

Excipient with known effect
This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.44 mmol of sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder for injection).
White to off-white powder.

Solvent: clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain in adults.

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

4.2 Posology and method of administration

Posology
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.

As the cardiovascular risk of 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. There is limited clinical experience with Dynastat treatment beyond three days (see section 5.1).

Concomitant use with opioid analgesics
Opioid analgesics can be used concurrently with parecoxib, dosing as described in the paragraph above. In all clinical assessments parecoxib was administered at a fixed time interval whereas the opioids were administered on as needed basis.

Elderly
No dose adjustment is generally necessary in elderly patients (≥65 years). However, for elderly patients weighing less than 50 kg, treatment should be initiated with half the usual recommended dose of Dynastat and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic impairment
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). No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Dynastat should be introduced with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and the maximum daily dose should be reduced to 40 mg.

Renal impairment
In patients with severe renal impairment (creatinine clearance <30 ml/min.) or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose (20 mg) and the patient's kidney function should be closely monitored (see sections 4.4 and 5.2). On the basis of pharmacokinetics, no dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min.).

Paediatric population
The safety and efficacy of parecoxib in children under 18 years old have not been established. No data are available. Therefore, parecoxib 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 medicinal product before administration, see section 6.6.

Precipitation may occur when Dynastat is combined in solution with other medicinal products and therefore Dynastat must not be mixed with any other medicinal product, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility.

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

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion; or
- Ringer-Lactate solution for injection.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome), toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulfonamides (see sections 4.4 and 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 nonsteroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors.

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

Severe hepatic impairment (serum albumin <25 g/l or Child-Pugh score ≥10).

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

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

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Dynastat has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is limited experience in other types of surgery, for example gastrointestinal or urological surgery (see section 5.1).

Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.

Because of the possibility for increased adverse reactions at higher doses of 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). There is limited clinical experience with Dynastat treatment beyond three days (see section 5.1).

If, during treatment, patients deteriorate in any of the organ system functions described below, appropriate measures should be taken and discontinuation of parecoxib therapy should be considered.

Cardiovascular
COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with parecoxib after careful consideration (see section 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. Dynastat has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft (CABG) procedures. Studies in types of surgery other than CABG procedures included patients with American Society of Anaesthesiology (ASA) Physical Status Class I-III only.

Acetylsalicylic acid and other NSAIDs
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). Caution should be exercised when coadministering Dynastat with warfarin and other oral anticoagulants (see section 4.5). The concomitant use of parecoxib with other non- acetylsalicylic acid NSAIDs should be avoided.

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.

Gastrointestinal
Upper gastrointestinal (GI) 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, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding, or patients using acetylsalicylic acid concomitantly. The NSAIDs class is also associated with increased GI complications when coadministered with glucocorticoids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or patients ingesting alcohol. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Skin reactions
Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib. Additionally, fatal reports of toxic epidermal necrolysis have been reported through post-marketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib (see section 4.8). Some NSAIDs and selective COX- 2 inhibitors have been associated with an increased risk of generalized bullous fixed drug eruptions (GBFDE). 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 reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment.

Appropriate measures should be taken by physicians to monitor for any serious skin reactions with therapy, e.g. additional patient consultations. Patients should be advised to immediately report any emergent skin condition to their physician.

Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors. Patients with a history of sulfonamide allergy may be at greater risk of skin reactions (see section 4.3). Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity
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 sulfonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

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 physician should be prepared to treat severe hypotension.

Fluid retention, oedema, renal
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, preexisting oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise

at risk of hypovolemia. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken.

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.

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. 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. If blood pressure rises significantly, alternative treatment should be considered.

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

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) (see section 4.5).

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium-free’.

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).

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

Inhibition of prostaglandins by NSAIDs, including COX-2 inhibitors, may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers and diuretics. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers and diuretics.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with

ACE inhibitors or Angiotensin-II antagonists, may result in further 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.

Coadministration of NSAIDs and ciclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus because of NSAID effects on renal prostaglandins. Renal function should be monitored when parecoxib and any of these medicinal products are coadministered.

Dynastat may be coadministered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when coadministered with parecoxib.

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 coadministered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib 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 coadministered 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 coadministered 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 coadministering 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 two pharmacokinetic interaction studies in rheumatoid arthritis patients receiving a stable weekly methotrexate dose (5-20 mg/week, as a single oral or intramuscular dose), orally administered valdecoxib (10 mg twice daily or 40 mg twice daily) had little or no effect on the steady-state plasma concentrations of methotrexate. However caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate. Adequate monitoring of methotrexate-related toxicity should be considered when coadministering parecoxib and methotrexate.

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 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 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 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 was administered pre-operatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib and the inhalation anaesthetic agents nitrous oxide and isoflurane (see section 5.1).

4.6 Fertility, pregnancy, and lactation

Pregnancy
There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality (see sections 5.1 and 5.3). From the 20th week of pregnancy onward, Dynastat use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Dynastat should not be given unless clearly necessary. If Dynastat is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Dynastat for several days from gestational week 20 onward. Dynastat should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Dynastat is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding
Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Dynastat must not be administered to women who breast-feed (see section 4.3).

Fertility
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 4.3, 5.1 and 5.3).

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 Dynastat should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence after receiving Dynastat should refrain from driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reaction for Dynastat is nausea. The most serious reactions occur uncommonly to rarely, and include cardiovascular events such as myocardial infarction and severe hypotension, as well as hypersensitivity events such as anaphylaxis, angioedema and severe skin reactions. Following coronary artery bypass graft surgery, patients administered Dynastat have a higher risk of adverse reactions such as: cardiovascular/thromboembolic events (including myocardial infarction, stroke/TIA, pulmonary embolus, and deep vein thrombosis; see sections 4.3 and 5.1), deep surgical infections, and sternal wound healing complications.

Tabulated list of adverse reactions
The following adverse reactions were reported for patients who received parecoxib (N=5,402) in 28 placebo-controlled clinical trials. Reports from post-marketing experience have been listed as "frequency not known" because the respective frequencies cannot be estimated from the available data. Within each frequency grouping, adverse reactions are listed using MedDRA terminology and presented in order of decreasing seriousness.

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Infections and infestations				
	Pharyngitis, alveolar osteitis (dry socket)	Abnormal sternal serous wound drainage, wound infection		
Blood and lymphatic system disorders				
	Anaemia postoperative	Thrombocytopenia		
Immune system disorders				
			Anaphylactoid reaction	
Metabolism and nutrition disorders				
	Hypokalaemia	Hyperglycaemia, anorexia		

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Psychiatric disorders				
	Agitation, insomnia			
Nervous system disorders				
	Hypoaesthesia, dizziness	Cerebrovascular disorder		
Ear and labyrinth disorders				
		Ear pain		
Cardiac disorders				
		Myocardial infarction, bradycardia		Circulatory collapse, congestive heart failure, tachycardia
Vascular disorders				
	Hypertension, hypotension	Hypertension (aggravated), orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders				
	Respiratory insufficiency	Pulmonary embolism		Dyspnoea
Gastrointestinal disorders				
Nausea	Abdominal pain, vomiting, constipation, dyspepsia, flatulence	Gastroduodenal ulceration, gastrooesophageal reflux disease, dry mouth, gastrointestinal sounds abnormal	Pancreatitis, oesophagitis, oedema mouth (perioral swelling)	
Skin and subcutaneous tissue disorders				
	Pruritus, hyperhidrosis	Ecchymosis, rash, urticaria		Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
Musculoskeletal and connective tissue disorders				
	Back pain	Arthralgia		
Renal and urinary disorders				
	Oliguria		Renal failure acute	Renal failure,
General disorders and administration site conditions				
	Oedema peripheral	Asthenia, injection site pain, injection site reaction		Hypersensitivity reactions including anaphylaxis and angioedema
Investigations				
	Blood creatinine increased	Blood CPK increased, blood LDH increased, SGOT increased, SGPT increased, BUN increased.		

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Not known*
Injury, poisoning and procedural complications				
		Post procedural complication (skin)		

Description of selected adverse reactions
In post-marketing experience, toxic epidermal necrolysis has been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib (see section 4.4). In addition, the following rare, serious adverse reactions have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: bronchospasm and hepatitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, Coxibs, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective 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.

Parecoxib has been used in a 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 7-13 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.

Use of parecoxib beyond 3 days

Most trials were designed for dosing of parecoxib up to 3 days. Data from 3 randomised placebo-controlled trials, where the protocols allowed treatment of parecoxib for >3 days was pooled and analysed. In the pooled analysis of 676 patients, 318 received placebo and 358 received parecoxib. Of the patients treated with parecoxib, 317 patients received parecoxib for up to 4 days, 32 patients for up to 5 days, while only 8 patients were treated for up to 6 days and 1 patient for 7 or more days. Of the patients treated with placebo, 270 patients received placebo for up to 4 days, 43 patients for up to 5 days, while only 3 patients were treated for up to 6 days and 2 patients for 7 or more 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 4-7 days for parecoxib and 4-9 days for placebo. The occurrence of adverse events in patients receiving parecoxib for 4-7 days (median duration 4 days) was low after treatment Day 3 and similar to placebo.

Opioid-sparing effects

In a placebo-controlled, orthopedic and general surgery study (n =1050), patients received Dynastat at an initial parenteral dose of 40 mg IV followed by 20 mg twice daily for a minimum of 72 hours in addition to receiving standard care including supplemental patient controlled opioids. The reduction in opioid use with Dynastat treatment on Days 2 and 3 was 7.2 mg and 2.8 mg (37% and 28% respectively). This reduction in opioid use was accompanied by significant reductions in patient-reported opioid symptom distress. Added pain relief compared to opioids alone was shown. Additional studies in other surgical settings provided similar observations. There are no data indicating less overall adverse events associated with the use of parecoxib compared to placebo when used in conjunction with opioids.

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

period (4.8% and 1.3% respectively). Surgical wound complications (most involving the sternal wound) were observed at an increased rate with parecoxib/valdecoxib treatment.

In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib 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/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 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 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.

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

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, the elimination half-life ($t_{1/2}$) of valdecoxib is about 8 hours.

Elderly
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 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 (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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib. 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 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 has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Disodium hydrogen phosphate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

Solvent
Sodium chloride
Hydrochloric acid or sodium hydroxide (for pH adjustment)
Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

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

Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is **not** recommended.

Use of water for injection is **not** recommended, as the resulting solution is not isotonic.

After reconstitution
Dynastat should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility (see section 6.6).

Injection of the reconstituted product into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in section 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

The shelf life of the unreconstituted product is 3 years.

Chemical and physical in-use stability of the reconstituted solution, which should not be refrigerated or frozen, have been demonstrated for up to 24 hours at 25°C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable products, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Parecoxib sodium vials
Type I colourless glass vials (5 ml) with a butyl rubber stopper, sealed with a purple polypropylene flip-off cap on the aluminium overseal.

Solvent ampoules
2 ml ampoule: colourless neutral glass, Type I.

Dynastat is supplied as a sterile, single unit-of-use vial that is packaged with a 2 ml ampoule with a fill volume of 2 ml sodium chloride 9 mg/ml (0.9%) solution (see below for various pack sizes and configurations)

Pack sizes
1 + 1 pack: contains 1 powder vial and 1 solvent ampoule.
3 + 3 pack: contains 3 powder vials and 3 solvent ampoules.
5 + 5 pack: contains 5 powder vials and 5 solvent ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Reconstitution solvents
Reconstitute Dynastat 40 mg with 2 ml sodium chloride 9 mg/ml (0.9%) solution.

The **only** other acceptable solvents for reconstitution are:

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

Reconstitution process
Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib).
Remove the purple flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, the liquid should be a clear solution. 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 for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion;

  or
- Ringer-Lactate solution for injection.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/006-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2002
Date of latest renewal: 24 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs-Sint-Amands
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 40 mg vials

CARTON TEXT - EU/1/02/209/005

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder for solution for injection
parecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. After reconstitution with 2 ml of solvent, the concentration of parecoxib is 20 mg/ml. Thus, each 2 ml of reconstituted solution contains 40 mg of parecoxib.

3. LIST OF EXCIPIENTS

Also contains disodium hydrogen phosphate, phosphoric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted product should be used immediately (up to 24 hours if prepared aseptically), and should not be frozen or refrigerated.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution. For more information on storage see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynastat 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL: 40 mg

TEXT FOR VIAL LABEL - EU/1/02/209/005

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dynastat 40 mg powder for injection
parecoxib
IV/IM

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON: 40 mg powder and solvent for solution for injection

CARTON TEXT - EU/1/02/209/006

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder and solvent for solution for injection
parecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. After reconstitution with 2 ml of solvent, the concentration of parecoxib is 20 mg/ml. Thus, each 2 ml of reconstituted solution provides 40 mg of parecoxib.

3. LIST OF EXCIPIENTS

Also contains disodium hydrogen phosphate, phosphoric acid and sodium hydroxide.

2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 vial and 1 solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted product should be used immediately (up to 24 hours if prepared aseptically), and should not be frozen or refrigerated.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution. For more information on storage see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynastat 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT: 40 mg powder and solvent for solution for injection

CARTON TEXT - EU/1/02/209/007

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder and solvent for solution for injection
parecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. After reconstitution with 2 ml of solvent, the concentration of parecoxib is 20 mg/ml. Thus, each 2 ml of reconstituted solution provides 40 mg of parecoxib

3. LIST OF EXCIPIENTS

Also contains disodium hydrogen phosphate, phosphoric acid and sodium hydroxide.

2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

3 vials and 3 solvent ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted product should be used immediately (up to 24 hours if prepared aseptically), and should not be frozen or refrigerated.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution. For more information on storage see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynastat 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT: 40 mg powder and solvent for solution for injection

CARTON TEXT - EU/1/02/209/008

1. NAME OF THE MEDICINAL PRODUCT

Dynastat 40 mg powder and solvent for solution for injection
parecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. After reconstitution with 2 ml of solvent, the concentration of parecoxib is 20 mg/ml. Thus, each 2 ml of reconstituted solution provides 40 mg of parecoxib

3. LIST OF EXCIPIENTS

Also contains disodium hydrogen phosphate, phosphoric acid and sodium hydroxide.

2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

5 vials and 5 solvent ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous or intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The reconstituted product should be used immediately (up to 24 hours if prepared aseptically), and should not be frozen or refrigerated.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution. For more information on storage see the package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynastat 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL: 40 mg

TEXT FOR VIAL LABEL - EU/1/02/209/006, EU/1/02/209/007 and EU/1/02/209/008

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dynastat 40 mg powder for injection
parecoxib
IV/IM

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT AMPOULE LABEL : 2 ml

TEXT FOR AMPOULE LABEL - EU/1/02/209/006, EU/1/02/209/007 and EU/1/02/209/008

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sodium chloride 9 mg/ml (0.9%) solution

2. METHOD OF ADMINISTRATION

Solvent for Dynastat 40 mg

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dynastat 40 mg powder for solution for injection
parecoxib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dynastat is and what it is used for

Dynastat contains the active substance parecoxib.

Dynastat is used for the short-term treatment of pain in adults after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for *cyclo-oxygenase-2 inhibitors*). Pain and swelling are sometimes caused by substances in the body called *prostaglandins*. Dynastat works by lowering the amount of these prostaglandins.

2. What you need to know before you use Dynastat

Do not use Dynastat
- if you are allergic to parecoxib or any of the other ingredients of this medicine (listed in section 6)
- if you have had a serious allergic reaction (especially a serious skin reaction) to any medicines
- if you have had an allergic reaction to a group of medicines called “sulfonamides” (e.g. some antibiotics used to treat infections)
- if you currently have a gastric or intestinal ulcer or bleeding in the stomach or gut
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breast-feeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have heart failure
- if you are about to have heart surgery or surgery on your arteries (including any coronary artery procedure)
- if you have established heart disease and /or cerebrovascular disease e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages
- if you have or have had problems with your blood circulation (peripheral arterial disease)

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

Warnings and precautions

Do not use Dynastat if you currently have a gastric or intestinal ulcer or gastrointestinal bleeding

Do not use Dynastat if you have severe liver disease

Talk to your doctor or nurse before using Dynastat:
- If you have previously had an ulcer, bleeding, or perforation of the gastrointestinal tract
- If you have had a skin reaction (e.g. a rash, hives, welts, blisters, red streaks) with any medicine
- If you are taking acetylsalicylic acid (aspirin), or other NSAIDs (e.g. ibuprofen)
- If you smoke or drink alcohol
- If you have diabetes
- If you have angina, blood clots, high blood pressure, or raised cholesterol
- If you are taking antiplatelet therapies
- If you have fluid retention (oedema)
- If you have liver or kidney disease
- If you are dehydrated – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- If you have an infection as it may hide a fever (which is a sign of infection)
- If you use medicines to reduce blood clotting (e.g. warfarin/warfarin like anticoagulants or novel oral anti-clotting medicines, e.g. apixaban, dabigatran, and rivaroxaban)
- If you use medicines called corticosteroids (e.g. prednisone)
- If you use a class of medicines used to treat depression called selective serotonin re-uptake inhibitors (e.g. sertraline)

Dynastat can lead to an increase in blood pressure or worsening of existing high blood pressure which may result in an increase in side effects associated with heart conditions. Your doctor may want to monitor your blood pressure during treatment with Dynastat.

Potentially life-threatening skin rashes may occur with the use of Dynastat and treatment should be discontinued at the first appearance of skin rash, blistering and peeling of the skin, mucosal lesions, or any other sign of hypersensitivity. If you develop a rash, other skin, or mucosal (such as inside of cheeks or lips) signs and symptoms, seek immediate advice from a doctor and tell them that you are taking this medicine.

Children and adolescents
Children and adolescents under the age of 18 should not be given Dynastat.

Other medicines and Dynastat
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Dynastat or other medicines, or you may need to take a different medicine. It's especially important to mention:
- Acetylsalicylic acid (aspirin) or other anti-inflammatory medicines
- Fluconazole – used for fungal infections
- ACE inhibitors, Angiotensin-II inhibitors, beta blockers and diuretics – used for high blood pressure and heart conditions
- Ciclosporin or Tacrolimus – used after transplants
- Warfarin – or other warfarin like medicines used to prevent blood clots including newer medicines like apixaban, dabigatran, and rivaroxaban
- Lithium – used to treat depression
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Methotrexate – used for rheumatoid arthritis and cancer

- Diazepam – used for sedation and anxiety
- Omeprazole – used for treating ulcers

Pregnancy, breast-feeding and fertility
- Dynastat must not be used if you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. Dynastat should not be used during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used. If used for more than a few days from 20 weeks of pregnancy onward, Dynastat can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.
- **If you are breast-feeding**, you must not receive Dynastat, as a small amount of Dynastat will be transferred to your breast milk.
- NSAIDs, including Dynastat, may make it more difficult to become pregnant. You should tell your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

Driving and using machines
If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

Dynastat contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml that is to say essentially 'sodium-free'.

3. How to use Dynastat

Dynastat will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. The injection may be given rapidly and directly into a vein or into an existing intravenous line (a thin tube running into a vein), or it can be given slowly and deeply into a muscle. You will only be given Dynastat for short periods, and only for pain relief.

The usual dose to start with is 40 mg.
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.

You will not be given more than 80 mg in 24 hours.

Some people may be given lower doses:
- People with liver problems
- People with severe kidney problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

If Dynastat is used with strong pain killers (called opioid analgesics) such as morphine the dose of Dynastat will be the same as explained above.

If you are given more Dynastat than you should you may experience side effects that have been reported with recommended doses.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Dynastat and tell your doctor immediately:
- if you develop a rash or ulceration in any part of your body (e.g. skin, mouth, eyes, face, lips or tongue), or develop any other signs of an allergic reaction such as skin rash, swelling of the face, lips or tongue which may cause wheezing, difficulty breathing, or swallowing (potentially fatal) – this occurs **rarely**
- if you have swelling, blistering or peeling of the skin – it is not known how frequently this occurs
- the onset of skin reactions can occur at any time but most often occur in the first month of treatment; the reported rate of these events appears to be greater for valdecoxib, a medicine related to parecoxib, as compared to other COX-2 inhibitors
- if you have jaundice (your skin or the whites of your eyes appear yellow)
- if you have any signs of bleeding in the stomach or intestine, such as passing a black or blood-stained bowel movement or vomiting blood

Very common: may affect more than 1 in 10 people
- Nausea (feeling sick)

Common: may affect up to 1 in 10 people
- Change in your blood pressure (up or down)
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb – your skin may lose sensitivity to pain and touch
- You may get vomiting, stomach ache, indigestion, constipation, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- Dizziness
- There is a risk of anaemia - changes in red blood cells after an operation that may cause fatigue and breathlessness
- You may get a sore throat or difficulty breathing (shortness of breath)
- Your skin may be itchy
- You may pass less urine than usual.
- Dry socket (inflammation and pain after a tooth extraction)
- Increased sweating
- Low levels of potassium in blood test results

Uncommon: may affect up to 1 in 100 people
- Heart attack
- There is a risk of cerebrovascular disease e.g. stroke, or transient ischaemic attack (transient reduced blood flow to the brain)/mini-stroke or angina, or blockages to blood vessels to the heart or brain
- Blood clot in the lungs
- Worsening of high blood pressure
- Ulcers in the digestive system, chronic stomach acid reflux
- The heart may beat more slowly
- Low blood pressure on standing
- Blood tests may show abnormal liver function
- You may bruise easily due to a low blood platelet count
- Surgical wounds may become infected, abnormal discharge from surgical wounds
- Skin discolouration or bruising
- Complications with skin healing after operations
- High sugar levels in blood tests

- Injection site pain or injection site reaction
- Rash, or raised itchy rash (hives)
- Anorexia (loss of appetite)
- Joint pain
- High levels of blood enzymes in blood tests that indicate injury or stress to the heart, the brain, or muscle tissue
- Dry mouth
- Muscle weakness
- Ear ache
- Unusual abdominal sounds

Rare: may affect up to 1 in 1,000 people
- Acute kidney failure
- Hepatitis (inflamed liver)
- Inflammation of the gullet (oesophagus)
- Inflammation of the pancreas (can lead to stomach pain)

Not known: frequency cannot be estimated from the available data
- Collapse due to severe low blood pressure
- Heart failure
- Kidney failure
- Racing or irregularity of the heartbeat
- Breathlessness

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dynastat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the vial label after Exp. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions prior to reconstitution.

It is recommended that Dynastat is used as soon as possible after it is mixed with solvent, although it may be stored if the instructions at the end of the leaflet are strictly followed.

The injection solution should be a clear colourless liquid. **If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.

6. Contents of the pack and other information

What Dynastat contains
- The active substance is parecoxib (as parecoxib sodium). Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. When reconstituted with 2 ml solvent, provides 20 mg/ml of parecoxib. When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.44 mEq of sodium per vial.

- The other ingredients are:

  Disodium hydrogen phosphate
  Phosphoric acid and/or sodium hydroxide (for pH adjustment).

What Dynastat looks like and contents of the pack
Dynastat is available as a white to off-white powder.
The powder is contained in colourless glass vials (5 ml) with a stopper, sealed with a purple flip-off cap on the aluminium overseal.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
Manufacturer: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only

Dosing. 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.

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

As the cardiovascular 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.

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 physician should be prepared to treat severe hypotension.

Administration is by intramuscular (IM) or intravenous (IV) injection. The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line.

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.

Reconstitution solvents
This medicinal product must not be mixed with other medicinal products. It is to be reconstituted only with one of the following:

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion; or
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion.

The following solutions **cannot** be used for reconstitution:

- Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (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 for reconstitution is not recommended, as the resulting solution is **not** isotonic.

Reconstitution process
Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).
40 mg vial: Remove the purple flip-off cap to expose the central portion of the rubber stopper of the parecoxib 40 mg vial. Withdraw with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 40 mg vial.

Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use.

The reconstituted solution must not be used if discoloured or cloudy or if particulate matter is observed.

The entire contents of the vial should be withdrawn for a single administration. If a dose lower than 40 mg is required, excess medicine should be discarded.
IV line solution compatibility

Precipitation may occur when Dynastat is combined in solution with other medicinal products and therefore Dynastat must not be mixed with any other drug, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility.

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

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion; or
- Ringer-Lactate solution for injection.

It is not recommended to inject the reconstituted product into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in this section, as this may cause precipitation from solution.

The solution is for single use only and must not be stored in a refrigerator or freezer.
Chemical and physical in-use stability of the reconstituted solution have been demonstrated for up to 24 hours at 25°C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable products, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-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.

Package leaflet: Information for the user

Dynastat 40 mg powder and solvent for solution for injection
parecoxib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dynastat is and what it is used for

Dynastat contains the active substance parecoxib.

Dynastat is used for the short-term treatment of pain in adults after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for *cyclo-oxygenase-2 inhibitors*). Pain and swelling are sometimes caused by substances in the body called *prostaglandins*. Dynastat works by lowering the amount of these prostaglandins.

2. What you need to know before you use Dynastat

Do not take Dynastat
- if you are allergic to parecoxib or any of the other ingredients of this medicine (listed in section 6)
- if you have had a serious allergic reaction (especially a serious skin reaction) to any medicines
- if you have had an allergic reaction to a group of medicines called “sulfonamides” (e.g. some antibiotics used to treat infections)
- if you currently have a gastric or intestinal ulcer or bleeding in the stomach or gut
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breast-feeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have heart failure
- if you are about to have heart surgery or surgery on your arteries (including any coronary artery procedure)
- if you have established heart disease and /or cerebrovascular disease e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages
- if you have or have had problems with your blood circulation (peripheral arterial disease)

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

Warnings and precautions

Do not use Dynastat if you currently have a gastric or intestinal ulcer or gastrointestinal bleeding

Do not use Dynastat if you have severe liver disease

Talk to your doctor or nurse before using Dynastat:

- If you have previously had an ulcer, bleeding or perforation of the gastrointestinal tract
- If you have had a skin reaction (e.g. a rash, hives, welts, blisters, red streaks) with any medicine
- If you are taking acetylsalicylic acid (aspirin) or other NSAIDs (e.g. ibuprofen)
- If you smoke or drink alcohol
- If you have diabetes
- If you have angina, blood clots, high blood pressure or raised cholesterol
- If you are taking antiplatelet therapies
- If you have fluid retention (oedema)
- If you have liver or kidney disease.
- If you are dehydrated – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- If you have an infection as it may hide a fever (which is a sign of infection)
- If you use medicines to reduce blood clotting (e.g. warfarin/warfarin like anticoagulants or novel oral anti-clotting medicines, e.g. apixaban, dabigatran, and rivaroxaban)
- If you use medicines called corticosteroids (e.g. prednisone)
- If you use a class of medicines used to treat depression called selective serotonin re-uptake inhibitors (e.g. sertraline)

Dynastat can lead to an increase in blood pressure or worsening of existing high blood pressure which may result in an increase in side effects associated with heart conditions. Your doctor may want to monitor your blood pressure during treatment with Dynastat.

Potentially life-threatening skin rashes may occur with the use of Dynastat and treatment should be discontinued at the first appearance of skin rash, blistering and peeling of the skin, mucosal lesions, or any other sign of hypersensitivity. If you develop a rash, other skin, or mucosal (such as inside of cheeks or lips) signs and symptoms, seek immediate advice from a doctor and tell them that you are taking this medicine.

Children and adolescents
Children and adolescents under the age of 18 should not be given Dynastat.

Other medicines and Dynastat
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Dynastat or other medicines, or you may need to take a different medicine. It's especially important to mention:

- Acetylsalicylic acid (aspirin) or other anti-inflammatory medicines
- Fluconazole – used for fungal infections
- ACE inhibitors, Angiotensin-II inhibitors, beta blockers and diuretics – used for high blood pressure and heart conditions
- Ciclosporin or Tacrolimus – used after transplants
- Warfarin – or other warfarin like medicines used to prevent blood clots including newer medicines like apixaban, dabigatran, and rivaroxaban
- Lithium – used to treat depression
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Methotrexate – used for rheumatoid arthritis and cancer

- Diazepam – used for sedation and anxiety
- Omeprazole – used for treating ulcers

Pregnancy, breast-feeding and fertility
- Dynastat must not be used if you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. Dynastat should not be used during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used. If used for more than a few days from 20 weeks of pregnancy onward, Dynastat can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.
- **If you are breast-feeding**, you must not receive Dynastat, as a small amount of Dynastat will be transferred to your breast milk.
- NSAIDs, including Dynastat, may make it more difficult to become pregnant. You should tell your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

Driving and using machines
If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

Dynastat contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

3. How to use Dynastat

Dynastat will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. The injection may be given rapidly and directly into a vein or into an existing intravenous line (a thin tube running into a vein), or it can be given slowly and deeply into a muscle. You will only be given Dynastat for short periods, and only for pain relief.

The usual dose to start with is 40 mg.
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.

You will not be given more than 80 mg in 24 hours.

Some people may be given lower doses:
- People with liver problems
- People with severe kidney problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

If Dynastat is used with strong pain killers (called opioid analgesics) such as morphine the dose of Dynastat will be the same as explained above.

If you are given more Dynastat than you should you may experience side effects that have been reported with recommended doses.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Dynastat and tell your doctor immediately:
- if you develop a rash or ulceration in any part of your body (e.g. skin, mouth, eyes, face, lips or tongue), or develop any other signs of an allergic reaction such as skin rash, swelling of the face, lips or tongue which may cause wheezing, difficulty breathing, or swallowing (potentially fatal) – this occurs **rarely**
- if you have swelling, blistering or peeling of the skin – it is not known how frequently this occurs
- the onset of skin reactions can occur at any time but most often occur in the first month of treatment; the reported rate of these events appears to be greater for valdecoxib, a medicine related to parecoxib, as compared to other COX-2 inhibitors
- if you have jaundice (your skin or the whites of your eyes appear yellow)
- if you have any signs of bleeding in the stomach or intestine, such as passing a black or blood-stained bowel movement or vomiting blood

Very common: may affect more than 1 in 10 people
- Nausea (feeling sick)

Common: may affect up to 1 in 10 people
- Change in your blood pressure (up or down)
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb – your skin may lose sensitivity to pain and touch
- You may get vomiting, stomach ache, indigestion, constipation, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- Dizziness
- There is a risk of anaemia - changes in red blood cells after an operation that may cause fatigue and breathlessness
- You may get a sore throat or difficulty breathing (shortness of breath)
- Your skin may be itchy
- You may pass less urine than usual.
- Dry socket (inflammation and pain after a tooth extraction)
- Increased sweating
- Low levels of potassium in blood test results

Uncommon: may affect up to 1 in 100 people
- Heart attack
- There is a risk of cerebrovascular disease e.g. stroke, or transient ischaemic attack (transient reduced blood flow to the brain)/mini-stroke or angina, or blockages to blood vessels to the heart or brain
- Blood clot in the lungs
- Worsening of high blood pressure
- Ulcers in the digestive system, chronic stomach acid reflux
- The heart may beat more slowly
- Low blood pressure on standing
- Blood tests may show abnormal liver function
- You may bruise easily due to a low blood platelet count
- Surgical wounds may become infected, abnormal discharge from surgical wounds
- Skin discolouration or bruising
- Complications with skin healing after operations
- High sugar levels in blood tests
- Injection site pain or injection site reaction

- Rash, or raised itchy rash (hives)
- Anorexia (loss of appetite)
- Joint pain
- High levels of blood enzymes in blood tests that indicate injury or stress to the heart, the brain, or muscle tissue.
- Dry mouth
- Muscle weakness
- Ear ache
- Unusual abdominal sounds

Rare: may affect up to 1 in 1,000 people
- Acute kidney failure
- Hepatitis (inflamed liver)
- Inflammation of the gullet (oesophagus)
- Inflammation of the pancreas (can lead to stomach pain)

Not known: frequency cannot be estimated from the available data
- Collapse due to severe low blood pressure
- Heart failure
- Kidney failure
- Racing or irregularity of the heartbeat
- Breathlessness

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dynastat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the vial label after Exp. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions prior to reconstitution.

It is recommended that Dynastat is used as soon as possible after it is mixed with solvent, although it may be stored if the instructions at the end of the leaflet are strictly followed.

The injection solution should be a clear colourless liquid. **If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.

6. Contents of the pack and other information

What Dynastat contains
- The active substance is parecoxib (as parecoxib sodium). Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. When reconstituted with 2 ml solvent, provides 20 mg/ml of parecoxib. When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.44 mEq of sodium per vial.

- The other ingredients are:
  Powder

Disodium hydrogen phosphate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

Solvent
Sodium chloride
Hydrochloric acid or sodium hydroxide (for pH adjustment)
Water for injection.

What Dynastat looks like and contents of the pack
Dynastat is available as a white to off-white powder.
The powder is contained in colourless glass vials (5 ml) with a stopper, sealed with a purple flip-off cap on the aluminium overseal.
The solvent is contained in colourless neutral glass ampoules (2 ml).

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
Manufacturer: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only

Dosing. 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.

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

As the cardiovascular 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.

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 physician should be prepared to treat severe hypotension.

Administration is by intramuscular (IM) or intravenous (IV) injection. The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line.

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.

Reconstitution solvents
This medicinal product must not be mixed with other medicinal products. It is to be reconstituted only with one of the following:

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion; or
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion.

The following solutions **cannot** be used for reconstitution:

- Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (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 for reconstitution is not recommended, as the resulting solution is **not** isotonic.

Reconstitution process
Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).
40 mg vial: Remove the purple flip-off cap to expose the central portion of the rubber stopper of the parecoxib 40 mg vial. Withdraw with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 40 mg vial.

Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use.

The reconstituted solution must not be used if discoloured or cloudy or if particulate matter is observed.

The entire contents of the vial should be withdrawn for a single administration. If a dose lower than 40 mg is required, excess medicine should be discarded.
IV line solution compatibility

Precipitation may occur when Dynastat is combined in solution with other medicinal products and therefore Dynastat must not be mixed with any other drug, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility.

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

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion; or
- Ringer-Lactate solution for injection.

It is not recommended to inject the reconstituted product into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in this section, as this may cause precipitation from solution.

The solution is for single use only and must not be stored in a refrigerator or freezer.
Chemical and physical in-use stability of the reconstituted solution have been demonstrated for up to 24 hours at 25°C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable products, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-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.