European Medicines Agency
*Press office*

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# EMEA PUBLIC STATEMENT ON VALDECOXIB (Bextra/Valdyn) and PARECOXIB SODIUM (Dynastat/Rayzon) CARDIOVASCULAR RISKS IN CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY AND SERIOUS ADVERSE SKIN REACTIONS

The European Medicines Agency (EMEA) and its Scientific Committee for human medicines have been made aware of new safety information on cardiovascular and serious skin adverse events in relation to the use of valdecoxib and parecoxib sodium.

## *Cardiovascular safety*

Two clinical studies were conducted to evaluate the safety of valdecoxib and parecoxib sodium, in patients following CABG surgery and another study in patients following general surgery.

The first CABG study evaluated the safety of parecoxib sodium/valdecoxib 40 mg BID given for up to 14 days in 462 patients (311 on parecoxib sodium/valdecoxib and 151 on placebo).

The second CABG surgery study evaluated parecoxib sodium (40mg then 20mg bid) /valdecoxib 20 mg bid or placebo/valdecoxib 20 mg bid or placebo/placebo for up to 10 days in 1671 patients (544 receiving parecoxib/valdecoxib, 544 placebo/valdecoxib and 548 placebo/placebo).

Both CABG studies showed a higher rate of serious cardiovascular thromboembolic events (e.g. myocardial infarction, cerebrovascular accident) in the parecoxib sodium/valdecoxib treatment arm compared to the group of patients receiving placebo. This was not observed in a general surgery setting.

## *Serious Skin Reactions*

The EMEA has received new post-marketing reports of serious skin reactions, some with fatal outcome, including *erythema multiforme*, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients receiving valdecoxib. *Erythema multiforme* has been reported in association with the use of parecoxib sodium.

The reported rate of these reactions appears to be greater for valdecoxib as compared with other COX-2 selective inhibitors.

Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first two weeks of treatment.

Patients without a history of sulphonamide allergy may also be at risk for serious skin reactions.

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**Based on the new data the EMEA wishes to point out the following information:**

***Information for physicians considering therapy of patients with valdecoxib or parecoxib:***

- Valdecoxib and parecoxib are contraindicated in patients following coronary artery bypass graft (CABG) surgery.
  - Prescribers are advised to carefully follow the latest version of the Summary of Product Characteristics, especially regarding the warnings and precautions in patients with a history of cardiovascular disease.

- In post-marketing experience serious skin adverse reactions most of which occurred within the first two weeks starting treatment, have been reported in association with valdecoxib. *Erythema multiforme* has been reported in association with the use of parecoxib sodium.
  - The reported rate of serious skin events appears to be greater for valdecoxib as compared to other COX-2 selective inhibitors.
  - Patients appear to be at highest risk for these events early in the course of therapy.
  - Patients without a history of sulphonamide allergy are also at risk for such reactions
  - Therapy should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

***Information for patients currently being treated with valdecoxib or parecoxib:***

- If you are about to have heart bypass surgery, please inform your physician, as you should not be given these medicines.

- These medicines already contain warnings regarding heart problems. If you have any concerns about your treatment, you are advised to consult your physician.

- If you develop itchy skin or ulceration of the skin, mouth, eyes, face, lips or tongue; or skin rash, swelling of the face, lips or tongue, or blistering and peeling, stop taking Bextra/Valdyn or Dynastat/Rayzon and tell your doctor, pharmacist or nurse immediately. Such allergic reactions often occur in the first weeks of treatment.

- The reported rate of serious skin events appears to be greater for valdecoxib as compared to other so-called COX-2 inhibitors.

The Product Information for valdecoxib and parecoxib sodium has now been modified to reflect the above-mentioned information and is appended to this press release.

--ENDS--

NOTES FOR EDITORS

1. COX-2 inhibitors (cyclo-oxygenase-2 inhibitors) are non-steroidal anti-inflammatory medicines (NSAID). They are approved in the European Union for use in a number of indications – see note 2 for information on the different products.

2. More information on these centrally authorised products can be found in the European Public Assessment Reports [here] for Bextra/Valdyn (valdecoxib), [here] for Dynastat/Rayzon (parecoxib).

3. This press release, together with other information about the work of the EMEA, may be found on the EMEA web site at the following location: http://www.emea.eu.int .

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**BEXTRA SPC WITH CHANGES HIGHLIGHTED AS ADOPTED BY THE CHMP ON 15 DECEMBER 2004 AS RELEVANT EXAMPLE (10 MG FILM-COATED TABLETS).**

## 1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg valdecoxib.

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets

White, capsule-shaped, debossed '10' on one side and '7815' on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis.
Treatment of primary dysmenorrhoea.

### 4.2 Posology and method of administration

Bextra is administered orally.
Bextra may be taken with or without food (see section 5.2).

*Osteoarthritis and rheumatoid arthritis:* The recommended dose is 10 mg once daily. Some patients may receive additional benefit from 20 mg once daily. The maximum recommended dose is 20 mg once daily.

*Treatment of primary dysmenorrhoea:* The recommended dose for symptomatic relief is 40 mg once daily as required. On the first day of treatment, an additional 40 mg dose may be taken if needed. Thereafter, the maximum recommended dose is 40 mg once daily.

*Elderly:* For elderly patients (≥ 65 years), in particular those of less than 50 kg body weight, initiate therapy at the lowest recommended dose for osteoarthritis and rheumatoid arthritis (10 mg once daily) (see section 5.2).

*Hepatic Impairment:* No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). In patients with moderate hepatic impairment (Child-Pugh score 7-9 ) treatment should be initiated with caution. The lowest recommended dose should be used for osteoarthritis and rheumatoid arthritis (10 mg once daily) and the dosage should not exceed 20 mg for primary dysmenorrhoea. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore use in such patients is contraindicated (see section 4.3 and 5.2).

*Renal Impairment:* On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate (creatinine clearance of 30-80 ml/min) or severe (creatinine clearance < 30

ml/min) renal impairment. However, caution should be observed in patients with renal impairment or patients who may be predisposed to fluid retention (see sections 4.4 and 5.2).

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

### 4.3 Contraindications

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

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

Active peptic ulceration or gastrointestinal (GI) bleeding.

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

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

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

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

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

### 4.4 Special warnings and special precautions for use

Because of the possibility for increased adverse reactions at higher doses of valdecoxib, other COX-2 inhibitors and NSAIDs, patients treated with valdecoxib 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).

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

There is an increased risk of gastrointestinal adverse effects for valdecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelet function. Because valdecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischaemia, coronary bypass graft surgery or peripheral vascular surgery) (see sections 4.5 and 5.1).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of valdecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients **(see section**

**5.1). Bextra has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft procedures.**

Serious skin reactions, **some of them fatal**, including **erythema multiforme**, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib (see section 4.8). **Patients appear to be at highest risk for these events early in the course of therapy; the onset of the event occurring in the majority of cases within the first 2 weeks of treatment.**

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

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

Caution should be exercised in patients with history of hypertension or cardiac failure or other conditions predisposing to fluid retention. Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering valdecoxib in patients with impaired renal function (see section 4.2). As with other NSAIDs, fluid retention, oedema and hypertension have been observed in some patients with chronic use of valdecoxib 10 – 20 mg/day (see section 5.1). These effects may be dose related and are seen more frequently at doses higher than those recommended for chronic administration. Valdecoxib should be introduced at the lowest recommended dose in patients with history of hypertension or cardiac failure or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with valdecoxib in patients with dehydration. In this case, it is advisable to rehydrate patients prior to starting therapy with valdecoxib.

Valdecoxib should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9) (see section 4.2 and 5.2).

Valdecoxib 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 non-clinical studies with valdecoxib (see section 5.3). Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving valdecoxib.

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

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

Bextra 10 mg, 20 mg and 40 mg film-coated tablets contain lactose (103 mg, 206 mg and 186 mg respectively). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malsorption should not take this medicine.

## 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 or changing valdecoxib therapy in patients receiving warfarin or other oral 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 valdecoxib is initiated or the dose of valdecoxib is changed (see section 4.4).

Valdecoxib had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times when parenterally administered as the prodrug, parecoxib sodium, with acetylsalicylic acid. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of valdecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see section 5.1).

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As with NSAIDs, the risk of acute renal insufficiency may be increased when valdecoxib is co-administered with ACE inhibitors or diuretics.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when valdecoxib and any of these medicinal products are co-administered.

**Effects of other medicinal products on the pharmacokinetics of valdecoxib**

In humans, valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isoenzymes. Therefore, co-administration of valdecoxib with medicinal products that are known to inhibit CYP3A4 and 2C9 should be done with caution.

Plasma exposure (AUC) to valdecoxib was increased 62% when co-administered with fluconazole (predominantly a CYP2C9 inhibitor) and 38% when co-administered with ketoconazole (CYP3A4 inhibitor). Valdecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole or ketoconazole therapy.

Following 12 days of co-administration of valdecoxib (40mg twice daily) with phenytoin (300 mg once daily), a CYP3A4 inducer, a 27% decrease in plasma exposure (AUC) of valdecoxib was observed. The decrease in valdecoxib plasma exposure was expected in view of the known enzyme-inducing properties of phenytoin and was not considered clinically significant, therefore an increase in the dose of valdecoxib when co-administered with phenytoin is not required. However, physicians should consider these results when administering valdecoxib with inducers of CYP3A4, such as carbamazepine and dexamethasone. Clinically significant reduction in valdecoxib AUC may occur when co-administered with stronger enzyme inducers such as rifampicin.

Administration of valdecoxib with antacid (aluminium magnesium hydroxide) had no significant effect on either the rate or extent of absorption of valdecoxib.

**Effect of valdecoxib on the pharmacokinetics of other medicinal products**

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

Plasma exposure of omeprazole (CYP2C19 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 valdecoxib with medicinal products known to be substrates of CYP2C19 (e.g. omeprazole, phenytoin, diazepam, or imipramine).

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

Co-administration of valdecoxib (40 mg twice daily for 7 days) 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 valdecoxib therapy in patients receiving lithium. Lithium carbonate (450 mg twice daily for 7 days) had no effect on valdecoxib pharmacokinetics.

Valdecoxib (40 mg twice daily) inhibited the metabolism of the combination oral contraceptive ethinyl estradiol (EE)/norethindrone (35 mcg/1 mg combination). Plasma exposures of EE and norethindrone were increased by 34% and 20% respectively. This increase in EE concentration should be considered when selecting an oral contraceptive for use with valdecoxib. An increase in EE exposure can increase the incidence of adverse reactions associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Co-administration of valdecoxib with glibenclamide (CYP3A4 substrate) did not affect either the glibenclamide's pharmacokinetics (exposure) nor pharmacodynamics (blood glucose and insulin levels).

*Injectable anaesthetics:* Neither the pharmacokinetics (metabolism and exposure) nor the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of intravenous propofol (CYP2C9 substrate) or intravenous midazolam (CYP3A4 substrate) were affected by valdecoxib following intravenous administration of the prodrug of valdecoxib, parecoxib sodium. Additionally, co-administration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP3A4-mediated metabolism of orally administered midazolam. Valdecoxib had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates) following co-administration with intravenous parecoxib sodium.

*Inhalation anaesthetics:* No formal interaction studies have been done. In studies in which valdecoxib was administered pre-operatively, no evidence of pharmacodynamic interaction was observed between valdecoxib and nitrous oxide or isoflurane (see section 5.1).

## 4.6 Pregnancy and lactation

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

The use of valdecoxib is contraindicated in the last trimester of pregnancy, because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia (see section 4.3, 5.1 and 5.3). Valdecoxib should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

There are no adequate data from the use of valdecoxib in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown.

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

## 4.7 Effects on ability to drive and use machines

No studies on the effect of valdecoxib on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence during treatment with valdecoxib should refrain from driving or operating machinery.

## 4.8 Undesirable effects

The clinical safety of valdecoxib has been evaluated in over 10, 000 patients, with over 2500 arthritis patients being treated for greater than 6 months and over 600 arthritis patients being treated for at least one year.

The following adverse events had a rate greater than placebo and have been reported among 4824 patients administered valdecoxib 10 mg to 40 mg as a single or multiple dose (up to 80 mg/day) in 24 placebo-controlled studies of acute pain (dental, gynaecologic, post-hernia repair, orthopaedic or coronary artery bypass graft surgery as well as primary dysmenorrhoea) or arthritis (osteoarthritis and rheumatoid arthritis). The discontinuation rates due to adverse events in the acute pain and arthritis studies were 2.3% and 6.8%, respectively, for patients receiving valdecoxib, and 1.6% and 6.0%, respectively, for patients receiving placebo.

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

*Infections and infestations*
Common: sinusitis, urinary tract infection
Uncommon: abnormal sternal serous wound drainage, wound infection, moniliasis, viral infection

*Blood and lymphatic system disorders*
Common: anaemia
Rare: thrombocytopenia, leukopenia

*Immune system disorders*
Uncommon: aggravated allergy

*Psychiatric disorders:*
Common: insomnia, somnolence
Uncommon: anxiety, confusion, nervousness
Rare: depression

*Nervous system disorders*
Uncommon: syncope, hypertonia, hypoaesthesia, paresthesia, taste perversion
Rare: dysphonia, cerebrovascular disorder

*Eye disorders*
Uncommon: periorbital swelling, blurred vision, conjunctivitis

*Cardiac disorders*
Uncommon: heart failure, palpitation

*Vascular disorders*
Common: hypertension,
Uncommon: aggravated hypertension, haematoma

*Respiratory, thoracic and mediastinal disorders*
Common: cough, pharyngitis
Uncommon: bronchospasm, pneumonia

*Gastrointestinal disorders*

Common: abdominal fullness, abdominal pain, alveolar osteitis, diarrhoea, dyspepsia, eructation, nausea, dry mouth
Uncommon: duodenitis, gastroenteritis, gastroduodenal ulceration, gastroesophogeal reflux, stomatitis
Rare: haematochezia, haematemesis, intestinal obstruction

*Skin and subcutaneous tissue disorders*
Common: pruritus, rash
Uncommon: ecchymosis, urticaria
Rare: angioedema, photosensitivity

*Renal and urinary disorders*
Uncommon: albuminuria, hematuria, oliguria
Rare: nephritis

*General disorders and administration site conditions*
Common: peripheral oedema
Uncommon: generalised oedema

*Investigations*
Uncommon: AST increased, ALT increased, alkaline phosphatase increased, BUN increased, creatinine increased, creatine phosphokinase increased, weight increased

Following coronary artery bypass graft surgery, patients taking valdecoxib have a higher risk of adverse **events**, such as **cardiovascular/thromboembolic events, deep surgical infections or** sternal wound **healing** complication**s. Cardiovascular/thromboembolic events include myocardial infarction, stroke/TIA, pulmonary embolus and deep vein thrombosis** (see section 4.**3 and 5.1**).

In post-marketing experience, the following reactions have been reported: anaphylactic reactions, angioedema, myocardial infarction, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4). The following rare, serious adverse events have been reported: acute renal failure, hepatitis, **hepatic failure,** pancreatitis.

### 4.9 Overdose

No case of overdose has been reported

In case of overdose, patients should be treated by symptomatic and supportive care. 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: Coxibs, ATC code: M01AH03

Valdecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thromboembolic 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.

*Osteoarthritis:* Valdecoxib was evaluated in six double-blind, randomised controlled trials in which approximately 2670 patients with osteoarthritis were treated for 6 to 52 weeks. Valdecoxib 10 mg and 20 mg once daily demonstrated significant improvement compared to placebo and was similar to naproxen 500 mg twice daily in a composite assessment of pain, stiffness and physical function measures in two 12-week studies of patients with osteoarthritis of the hip or knee, and relief of arthritis pain was reported within 24 hours of the first dose. In a 26 week study in patients with osteoarthritis of the knee or hip (some of whom also had osteoarthritis of the hand and/or spine), valdecoxib 10 mg and 20 mg once daily was shown to be clinically comparable to diclofenac 75 mg twice daily.

*Rheumatoid arthritis:* Valdecoxib was evaluated in five double-blind, randomised controlled trials in which 2684 patients were treated with valdecoxib for 6 to 26 weeks. Valdecoxib 10 mg and 20 mg was shown to be superior to placebo and similar to naproxen 500 mg twice daily in two 12-week studies using a composite of clinical, laboratory and functional measures in rheumatoid arthritis as well as reductions in joint pain and tenderness. In a 26 week study, valdecoxib 20 mg and 40 mg once daily was shown to be similar in effectiveness to diclofenac 75 mg twice daily. However, valdecoxib 40 mg did not provide additional benefit over valdecoxib 20 mg. Valdecoxib has been used effectively in combination with corticosteriods and/or DMARDS, such as methotrexate, gold salts and hydroxychloroquine.

*Primary dysmenorrhoea*: In primary dysmenorrhoea the majority of patients required only a single 40 mg dose of valdecoxib to relieve menstrual pain.

*Gastrointestinal studies:* In two 12-week studies of 1866 osteoarthritis patients, the incidence of endoscopically observed gastroduodenal ulcers with valdecoxib 10 mg and 20 mg once daily (3-7%) was statistically significantly lower than naproxen 500 mg twice daily (13%), ibuprofen 800 mg three times daily (16%) or diclofenac 75 mg twice daily (17%). The incidence rate for placebo was 6-7%.

In a 26 week study in which endoscopy was performed at 14 weeks in 1217 osteoarthritis or rheumatoid arthritis patients receiving valdecoxib 20 mg and 40 mg twice daily or naproxen 500 mg twice daily, the rate of gastroduodenal ulcers was significantly lower in patients receiving either dose of valdecoxib (4 and 8%, respectively) compared to those patients receiving naproxen (18%). In a second 26 week study in which endoscopy was performed only at the end of study in 722 rheumatoid arthritis patients receiving valdecoxib 20 mg and 40 mg once daily or diclofenac 75 mg twice daily, the rate of gastroduodenal ulcers was significantly lower in those patients receiving either dose of valdecoxib (4-6%) when compared to the diclofenac treated patients (16%).

In a prospective analysis of 7434 osteoarthritis and rheumatoid arthritis patients enrolled in 8 controlled studies of 12-26 weeks in duration, the annualised incidence of ulcer complications (gross bleeding, perforation or obstruction) with valdecoxib 5-80 mg/day was significantly lower (0.67%) than the annualised incidence observed with the NSAID comparators (1.97%) naproxen 500 mg twice daily, ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily. Although numerically higher, valdecoxib 5-80 mg/day was not statistically significantly different from placebo (0.0%). The therapeutic dose range in osteoarthritis and rheumatoid arthritis is 10-20 mg daily.

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

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

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

**In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib initial dose of 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=544) for the remainder of a 10 day treatment period; placebo IV followed by valdecoxib PO (n=544); or placebo IV followed by placebo PO (n=548). A significantly (p=0.033) greater incidence of events in the cardiovascular/thromboembolic category was detected in the parecoxib /valdecoxib treatment group (2.0%) compared to the placebo/placebo treatment group (0.5%). Placebo/valdecoxib treatment was also associated with a higher incidence of CV thromboembolic events versus placebo treatment, but this difference did not reach statistical significance. Three of the six cardiovascular thromboembolic events in the placebo/valdecoxib treatment group occurred during the placebo treatment period; these patients did not receive valdecoxib. Pre-specified events that occurred with the highest incidence in all three treatment groups involved the category of surgical wound complications, including deep surgical infections and sternal wound healing events.**

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

***General Surgery Safety Studies*: In a large (N=1050) major orthopedic/general surgery trial, patients received an initial dose of parecoxib 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=525) for the remainder of a 10 day treatment period, or placebo IV followed by placebo PO (n=525). There were no significant differences in the overall safety profile, including the four pre-specified event categories described above for the second CABG surgery study, for parecoxib sodium/valdecoxib compared to placebo treatment in these post-surgical patients.**

*Renal effects*: The renal effects of valdecoxib compared with placebo and conventional NSAIDs were assessed by prospectively designed pooled analyses of pre-defined renal events from five placebo-and active-controlled 12-week arthritis trials that included 1806 osteoarthritis or rheumatoid arthritis patients given valdecoxib 10 mg or 20 mg daily. The incidence of renal events observed in this analysis with valdecoxib 10 mg or 20 mg daily (3-4%), ibuprofen 800 mg three times daily (7%), naproxen 500 mg twice daily (2%) and diclofenac 75 mg twice daily (4%) were significantly higher than placebo-treated patients (1%). In all treatment groups, the majority of renal events were either due to the occurrence of oedema or worsening blood pressure.

*Platelet studies:* In a series of small, multiple dose studies in healthy young and elderly (≥65 years) subjects, single and multiple doses up to 7 days of valdecoxib 10 mg to 40 mg twice daily had no effect on platelet aggregation or bleeding time compared to placebo.

## 5.2 Pharmacokinetic properties

### Absorption

Valdecoxib is rapidly absorbed, achieving maximal plasma concentrations in approximately 3 hours. Valdecoxib's absolute bioavailability is 83% following oral administration. Food had no significant effect on either the peak plasma concentration ($C_{max}$) or extent of absorption (AUC) when valdecoxib was given with a high-fat meal, however, the time to peak plasma concentration ($T_{max}$) was delayed by 1-2 hours. Administration of valdecoxib with an antacid (aluminium magnesium hydroxide) had no significant effect on either the rate or extent of absorption of valdecoxib.

Bioavailability of valdecoxib given orally was not clinically significantly different compared to valdecoxib given intravenously as the prodrug parecoxib sodium.

Approximate dose proportionality in valdecoxib plasma exposure (AUC) was demonstrated after single doses of valdecoxib. With multiple doses (up to 100 mg/day for 14 days), valdecoxib AUC increases in a non-linear fashion at doses above 10 mg twice daily. Relative to AUC observed with single doses, these non-linear increases of 25-45% were not considered clinically significant and require no dosage reduction. Steady state plasma concentrations of valdecoxib are achieved prior to day 4.

### Distribution

The apparent volume of distribution of valdecoxib is approximately 55 litres. Plasma protein binding (mostly to albumin) is about 98% and is concentration independent over the range (21-2384 ng/ml). Valdecoxib and its active metabolite are preferentially partitioned into erythrocytes resulting in a blood to plasma ratio of about 2.

Valdecoxib has been shown to cross the placenta in rats and rabbits. Valdecoxib is also present in the cerebrospinal fluid of rats.

### Metabolism

Valdecoxib undergoes extensive hepatic metabolism involving multiple pathways, including cytochrome P-450 (CYP)-dependent (CYP3A4 and CYP2C9) isoenzymes as well as direct glucuronidation of the sulphonamide moiety. On multiple dosing, there is no clinically significant auto-induction of valdecoxib metabolism.

One active metabolite of valdecoxib has been identified in human plasma at approximately 10% the concentration of valdecoxib. This metabolite, which is a less potent COX-2 selective inhibitor than the parent, also undergoes extensive metabolism and constitutes less than 2% of the valdecoxib dose excreted in the urine and faeces. It exhibits approximately linear kinetics on multiple dosing and has an elimination half-life similar to valdecoxib. Because of its low concentration in the systemic circulation, it is not considered to contribute significantly to the safety or efficacy profile of valdecoxib.

### Elimination

Valdecoxib is eliminated predominantly via hepatic metabolism with less than 5% of the dose excreted unchanged in the urine and faeces. About 70% of the dose is excreted in the urine as inactive metabolites, about 20% as valdecoxib N-glucuronide. The elimination half-life ($t_{1/2}$) is approximately 8-11 hours and plasma clearance approximately 6L/h.

### Elderly

Valdecoxib has been administered to 2500 elderly patients (65-92 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 (AUC) 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**

Because renal elimination of valdecoxib is not important to its disposition, no clinically significant changes in valdecoxib clearance were found in patients with severe renal impairment or in patients undergoing haemodialysis. In addition, valdecoxib administration did not result in a significant change in average creatinine clearance in patients with mild to severe renal impairment (see section 4.2).

**Hepatic Impairment**

The lowest recommended dose should be used for osteoarthritis and rheumatoid arthritis (10 mg once daily) and the dosage should not exceed 20 mg daily for primary dysmenorrhoea, since valdecoxib plasma exposure was significantly increased (130%) in patients with moderate hepatic impairment compared to patients with normal hepatic function. Patients with severe hepatic impairment have not been studied, and therefore the use of valdecoxib in patients with severe hepatic impairment is contraindicated (see sections 4.2 and 4.3).

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

In repeated dose toxicity studies, adverse effects were seen in the gastrointestinal tract and kidneys, as with other COX inhibitors, and occurred at 2- to 5-fold the chronic human therapeutic exposure at 20 mg/day. In these studies, systemic exposure of valdecoxib increased with duration of dosing and was associated with an increase in adverse effects observed. Valdecoxib treatment was associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, reduced ovulation, implantation and number of live foetuses (increased pre- and post-implantation losses and a tendency to increased early resorptions) were seen in rats, in the absence of maternal toxicity, at valdecoxib exposure levels similar to that of the chronic human therapeutic exposure at 20 mg/day. The effects on ovulation were shown to be reversible. Exposure to valdecoxib did not impair male rat fertility including sperm count, motility or sperm morphology.

Valdecoxib is not considered teratogenic in rat and rabbit. However in the rabbit, increased incidence of resorption, reduced litter size, slightly reduced foetal weight and a possibly treatment-related increased incidence of skeletal malformations occurred at doses not producing maternal toxicity.

Lactating rats administered valdecoxib as a single dose showed concentrations of valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.
In a rat peri/postnatal study, there was an increased incidence of postnatal pup mortality at approximately 5- to 7-fold the human therapeutic exposure at 20 mg/day. Increased gestation length was seen in all groups exposed to valdecoxib.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, pregelatinised starch (maize), croscarmellose sodium and magnesium stearate.

The film-coat contains titanium dioxide (E171), hypromellose (E464), macrogol 400, polysorbate 80 (E433).

## 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

No special precautions for storage.

### 6.5 Nature and contents of container

2 tablets
5 tablets
10 tablets
20 tablets
30 tablets
50 tablets
100 tablets
PVC/aluminium foil blisters

30 x 1 tablets
100 x 1 tablets
100 x 1 (5 packs of 20 x 1) tablets
PVC/aluminium perforated unit dose blisters

300 tablets
500 tablets
HDPE bottles

Not all pack sizes may be marketed.

### 6.6 Instructions for use and handling and disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/001-010, 25-26

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 March 2003

## 10. DATE OF REVISION OF THE TEXT

**BEXTRA PL WITH CHANGES HIGHLIGHTED AS ADOPTED BY THE CHMP ON 15 DECEMBER 2004 AS RELEVANT EXAMPLE (10 MG FILM-COATED TABLETS)**

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**What's in this leaflet**:


**Bextra 10 mg film-coated tablets**
**Valdecoxib**
The active substance in Bextra is valdecoxib.
Bextra film-coated tablets contain 10 mg valdecoxib.

The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch (maize), croscarmellose sodium, and magnesium stearate. The coating of the tablet contains titanium dioxide (E171), hypromellose (E464), macrogol, polysorbate (E433).

**Marketing Authorisation Holder:**
Pharmacia-Pfizer EEIG, Sandwich, Kent, CT13 9NJ, United Kingdom

**Manufacturer:**
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Heinrich Mack Nachf. GmbH & Co., KG, Heinrich-Mack-Str. 35, D-89257, Illertissen, Germany

## 1. WHAT BEXTRA IS AND WHAT IT IS USED FOR

**What Bextra is:**
Your body makes substances called prostaglandins. Some prostaglandins cause pain and swelling, whilst others help protect the stomach lining. Bextra works by reducing the amount of prostaglandins which produce pain and swelling without reducing the protective prostaglandins in the stomach.

Bextra treats pain and inflammation. It belongs to a group of medicines called Coxibs that act by inhibiting cyclooxygenase-2 (COX-2).

Bextra 10 mg film-coated tablets are white, capsule-shaped and are marked with '10' on one side and '7815' on the other side.

Bextra film-coated tablets are available in the following pack sizes:

Blister packs of: 2, 5, 10, 20, 30, 50 and 100 film-coated tablets
Unit dose blister packs of: 30x1, 100x1 and 100x1(5 packs of 20x1) film-coated tablets
Bottle: 300 and 500 film-coated tablets

Not all pack sizes may be marketed.

**Osteoarthritis and rheumatoid arthritis:** Bextra is used to relieve the pain and swelling caused by osteoarthritis and rheumatoid arthritis.

**Primary dysmenorrhoea (menstrual pain and cramping):** Bextra is used to treat menstrual pain and cramping.

## 2. BEFORE YOU USE BEXTRA

**Do not use Bextra:**
- if you are hypersensitive (allergic) to valdecoxib or any of the other ingredients of Bextra
- if you have had an allergic reaction to a group of medicines called "sulphonamides" (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- if you have had asthma or 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 breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn's disease)
- if you have severe heart failure
- **if you are about to have heart surgery**

**Talk to your doctor first before using Bextra**

**Make sure your doctor knows** before you start taking Bextra:
- if you have had an ulcer, bleeding or perforation of the gastrointestinal tract
- if you are taking acetylsalicylic acid or other NSAIDs (e.g. ibuprofen)
- if you are taking anti-platelet therapies (e.g. acetylsalicylic acid)
- if your heart, liver or kidneys are not working well
- if your blood pressure is high, or if you have had a stroke **or if you have peripheral vascular disease**
- if you have fluid retention (oedema, such as swollen ankles and feet)
- if you are dehydrated, for instance due to sickness, diarrhoea or the use of diuretics
- if you have an infection, as it may hide fever (which is a sign of infection)
- if you use medicines to reduce blood clotting (e.g. warfarin)
- if you are trying to become pregnant or are pregnant

**Using Bextra with food and drink:**
Bextra may be taken with or without food.

**Pregnancy and Breast-feeding**
Like other medicines including aspirin or other NSAID medicines, if you are pregnant or thinking of becoming pregnant, you must inform your doctor before using Bextra. Do not use Bextra if you are more than 6 months pregnant. If you are breast-feeding, you must not use Bextra, as it is not known whether valdecoxib passes into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
If you feel dizzy or tired after using Bextra, do not drive or use heavy machinery until you feel better again.

**Information for patients intolerant of lactose, one of the ingredients of Bextra:**
Bextra contains lactose and should not be taken by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malsorption

**Using other medicines:**
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Medicines can sometimes affect the way that other medicines work. You may need to reduce the amounts of Bextra or other medicines. Your doctor will advise you. Tell your doctor if you are taking any of the following medicines:

- Acetylsalicylic acid or other anti-inflammatory drugs
- Fluconazole or ketoconazole (used to treat fungal infections)
- ACE inhibitors (for high-blood pressure and heart failure)
- Diuretics (water tablets used to treat fluid retention)
- Cyclosporin and tacrolimus (used for immune system suppression e.g. after transplants)
- Warfarin (used to prevent blood from clotting)
- Lithium (used to treat depression)
- Rifampicin (used to treat bacterial infections)
- Antiarrhythmics (for irregular heartbeat)
- Phenytoin or carbamazepine (for epilepsy)
- Theophylline (for asthma)
- Methotrexate (for rheumatoid arthritis and cancer)
- Neuroleptics (used to treat psychoses)
- Omeprazole (used to treat gastric ulcers and oesophageal reflux disease)

Bextra can be used in combination with low dose acetylsalicylic acid.

## 3. HOW TO USE BEXTRA

Always take Bextra exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of Bextra is too strong or too weak, talk to your doctor or pharmacist.

**Recommended dose**
Bextra is for adults only; it is not for use in children.

**For osteoarthritis and rheumatoid arthritis** the recommended dose is 10 mg taken once a day. The maximum dose is 20 mg once daily. Bextra should be taken each day for as long as your doctor prescribes. Bextra will not cure your condition, but it should help to control pain, swelling and stiffness.

**For treatment of menstrual pain** the recommended dose is 40 mg taken once a day as required. On the first day you may take an additional 40 mg dose if needed. Only take 80 mg in total on the first day of treatment and after that only 40 mg once daily.

**It is important that you take your tablets as your doctor has instructed.**

**Elderly patients:**
If you are over 65 years of age and especially if you weigh less than 50 kg, you may not eliminate valdecoxib as quickly from your body. Your doctor may start you at the lowest recommended dose.

**Liver problems:**
If you have liver problems your doctor may start with the lowest recommended dose of Bextra for osteoarthritis and rheumatoid arthritis (10 mg once a day) and the dosage should not exceed 20 mg for primary dysmenorrhoea.

**Other medicines:**
Your doctor may prescribe a lower dose of Bextra if you are taking medicines called fluconazole or ketoconazole (see section "Using other medicines").

**If you take more Bextra than you should:**
Immediately contact your doctor, pharmacist or hospital.

**If you forget to take Bextra:**
If you forget to take a tablet, take it as soon as you remember. If it is almost time for your next tablet, do not take the tablet that you have missed. Thereafter, continue to use Bextra as your doctor had prescribed. Do not take a double dose to make up for forgotten individual doses.

**Effects when treatment with Bextra is stopped:**
Unless your doctor tells you to stop your treatment, it is important to keep taking Bextra as your doctor has prescribed.

## 4. POSSIBLE SIDE-EFFECTS

Like all medicines, Bextra can have side-effects for some people. If you are worried about side-effects, talk to your doctor as some of these effects may be serious enough to require immediate medical attention.

**Stop taking Bextra 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 difficulty breathing, or wheezing
- if you have blistering or peeling of the skin
- **the onset of skin reactions can occur at any time but most often occur in the first 2 weeks of treatment; the reported rate of these events appears to be greater for valdecoxib 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

**More common side-effects which may affect more than 1 person in 100 are listed below:**
- Stomach ache, indigestion, diarrhoea, nausea, bloating and wind
- Itchy skin or rash
- Ankles, legs and feet may swell (fluid build-up)
- Raised blood pressure
- Dry mouth
- Dry socket **(inflammation and pain** after a tooth extraction**)**
- Coughing
- Swollen sinuses, sore throat
- Anaemia
- Sleepiness or problems sleeping
- Urinary infections

**Less common side-effects which may affect up to 1 person in 100 are listed below:**
- Worsening of high blood pressure, dizziness
- General fluid build up in the body, swelling of/or around the eyes, aggravated allergy
- Surgical wounds may become infected

- Increased muscle tension, numbness
- Swelling of the mouth or stomach lining, heartburn
- Palpitation (awareness of your heart beat)
- Abnormalities in liver or kidney function tests
- Weight gain
- Bruising
- Nervousness, anxiety, confusion
- Hives
- Changes in the way things taste
- Blurred vision
- Wheezing
- Upper-respiratory tract infections
- Ulcers or bleeding
- Heart failure

**Rare side-effects which may affect up to 1 person in 1000 are listed below:**

- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin
- Hoarse voice
- Obstruction of the digestive system
- Decrease in white blood cell and platelet counts
- Depression
- Sensitivity to light
- Inflammation of the kidney
- Stroke
- Kidney failure
- Hepatitis (inflamed liver)
- **Hepatic failure (liver failure)**
- Pancreatitis (inflamed pancreas)

If you are concerned about side-effects or notice any effects not mentioned in this leaflet, tell your doctor or pharmacist.

## 5. STORING BEXTRA

Keep out of the reach and sight of children.

There are no special precautions for storage.

Do not use Bextra film-coated tablets after the expiry date stated on the box, blister strip or bottle.

## 6. FURTHER INFORMATION

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 approved on**

**DYNASTAT SPC WITH CHANGES HIGHLIGHTED AS ADOPTED BY THE CHMP ON 15 DECEMBER 2004 AS RELEVANT EXAMPLE (20 MG POWDER FOR SOLUTION FOR INJECTION)**

## 1. NAME OF THE MEDICINAL PRODUCT

Dynastat 20 mg powder for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

### 4.2 Posology and method of administration

The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle. (see section 6.6 for instructions for reconstitution)

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

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

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

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

## 4.3 Contraindications

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

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

Active peptic ulceration or gastrointestinal (GI) bleeding.

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

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

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

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

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

## 4.4 Special warnings and special precautions for use

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

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

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

There is an increased risk of gastrointestinal adverse effects for parecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelet function. Because parecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischaemia, coronary bypass graft surgery or peripheral vascular surgery)– (see sections 4.5 and 5.1).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients **(see section**

**5.1). Dynastat has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft procedures.**

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

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

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

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

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

Dynastat should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)
Dynastat may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Dynastat. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Dynastat.

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

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

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

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

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

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Dynastat with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

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

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

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

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

*Inhalation anaesthetics:* No formal interaction studies have been done. In surgery studies in which parecoxib sodium was administered pre-operatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib sodium and the inhalation anaesthetic agents nitrous oxide and isoflurane. (see section 5.1)

## 4.6 Pregnancy and lactation

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

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

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

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

*Infections and infestations*
Uncommon: abnormal sternal serous wound drainage, wound infection.

*Blood and lymphatic system disorders*
Common: post-operative anaemia
Uncommon: thrombocytopenia

*Metabolism and nutrition disorders*
Common: hypokalaemia

*Pyschiatric disorders:*
Common: agitation, insomnia

*Nervous system disorders*
Common: hypoaesthesia
Uncommon: cerebrovascular disorder

*Cardiac disorders*
Uncommon: bradycardia

*Vascular disorders*
Common: hypertension, hypotension
Uncommon: aggravated hypertension

*Respiratory, thoracic and mediastinal disorders*
Common: pharyngitis, respiratory insufficiency

*Gastrointestinal disorders*
Common: alveolar osteitis (dry socket), dyspepsia, flatulence
Uncommon: gastroduodenal ulceration

*Skin and subcutaneous tissue disorders*
Common: pruritus
Uncommon: ecchymosis

*Musculoskeletal and connective tissue disorders*
Common: back pain

*Renal and urinary disorders*
Common: oliguria

*General disorders and administration site conditions*
Common: peripheral oedema

*Investigations*
Common: blood creatinine increased
Uncommon: SGOT increased, SGPT increased, blood urea nitrogen increased.

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

Following coronary artery bypass graft surgery, patients administered Dynastat have a higher risk of adverse events, such as **cardiovascular/ thromboembolic events, deep surgical infections and**

sternal wound **healing** complication**s. Cardiovascular/thromboembolic events include myocardial infarction, stroke/TIA, pulmonary embolus and deep vein thrombosis** (see section 4.**3 and 5.1**).

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

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

### 4.9 Overdose

No case of parecoxib overdose has been reported.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

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

The efficacy of Dynastat was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Dynastat. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

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

***CABG post-operative Safety Studies:*** **In addition to routine adverse event reporting, pre-specified event categories, adjudicated by an independent expert committee, were examined in two**

**placebo-controlled safety studies in which patients received parecoxib sodium for at least 3 days and then were transitioned to oral valdecoxib for a total duration of 10-14 days. All patients received standard of care analgesia during treatment.**

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

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

**In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib initial dose of 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=544) for the remainder of a 10 day treatment period; placebo IV followed by valdecoxib PO (n=544); or placebo IV followed by placebo PO (n=548). A significantly (p=0.033) greater incidence of events in the cardiovascular/thromboembolic category was detected in the parecoxib /valdecoxib treatment group (2.0%) compared to the placebo/placebo treatment group (0.5%). Placebo/valdecoxib treatment was also associated with a higher incidence of CV thromboembolic events versus placebo treatment, but this difference did not reach statistical significance. Three of the six cardiovascular thromboembolic events in the placebo/valdecoxib treatment group occurred during the placebo treatment period; these patients did not receive valdecoxib. Pre-specified events that occurred with the highest incidence in all three treatment groups involved the category of surgical wound complications, including deep surgical infections and sternal wound healing events.**

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

***General Surgery:*** **In a large (N=1050) major orthopedic/general surgery trial, patients received an initial dose of parecoxib 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=525) for the remainder of a 10 day treatment period, or placebo IV followed by placebo PO (n=525). There were no significant differences in the overall safety profile, including the four pre-specified event categories described above for the second CABG surgery study, for parecoxib sodium/valdecoxib compared to placebo treatment in these post-surgical patients.**

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

## 5.2 Pharmacokinetic properties

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

*Absorption*
Exposure of valdecoxib following single doses of Dynastat, as measured by both the area under the plasma concentration vs. time curve (AUC) and peak concentration ($C_{max}$), is approximately linear in the range of clinical doses. AUC and $C_{max}$ following twice daily administration is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with twice daily dosing.

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

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

*Metabolism*
Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) of the sulphonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10% of the concentration of valdecoxib; because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium.

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

*Elderly Subjects:* Dynastat has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. In healthy elderly subjects, the apparent oral clearance of valdecoxib was reduced, resulting in an approximately 40% higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted for body weight, steady state plasma exposure of valdecoxib was 16% higher in elderly females compared to elderly males. (see section 4.2)

*Renal Impairment:* In patients with varying degrees of renal impairment administered 20 mg IVDynastat, parecoxib was rapidly cleared from plasma. Because renal elimination of valdecoxib is not important to its disposition, no changes in valdecoxib clearance were found even in patients with severe renal impairment or in patients undergoing dialysis. (see section 4.2)

*Hepatic Impairment:* Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh score 7-9), treatment should be initiated with half the usual recommended dose of Dynastat and the

maximum daily dose should be reduced to 40 mg since valdecoxib exposures were more than doubled (130%) in these patients. Patients with severe hepatic impairment have not been studied and therefore the use of Dynastat in patients with severe hepatic impairment is not recommended. (see sections 4.2 and 4.3)

### 5.3 Preclinical safety data

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

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

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

The carcinogenic potential of parecoxib sodium has not been evaluated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

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

### 6.2 Incompatibilities

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

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

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

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

Do not inject Dynastat into an IV line delivering any other drug. The IV line must be adequately flushed prior to and after Dynastat injection with a solution of known compatibility (see section 6.6)

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

## 6.3 Shelf life

3 years.

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

## 6.4 Special precautions for storage

No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

## 6.5 Nature and contents of container

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

Dynastat is available in packs containing 10 vials.

## 6.6 Instructions for use and handling <and disposal>

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

**Reconstitution solvents**
Acceptable solvents for reconstitution of Dynastat are:

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

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

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

The reconstituted product is isotonic.
**IV line solution compatibility**
After reconstitution with acceptable solvents, Dynastat may **only** be injected IV or IM, or into IV lines delivering:

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

Ringer-Lactate solution for injection

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

## 7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/209/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22nd March 2002

## 10. DATE OF REVISION OF THE TEXT

**DYNASTAT PL WITH CHANGES HIGHLIGHTED AS ADOPTED BY THE CHMP ON 15 DECEMBER 2004 AS RELEVANT EXAMPLE (20 MG POWDER FOR SOLUTION FOR INJECTION)**

**Read all of this leaflet carefully before you are given this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

**What's in this leaflet**:


**Dynastat** 20 mg powder for solution for injection

**The active substance** in Dynastat is parecoxib 20 mg/vial (as 21.18 mg parecoxib sodium). After reconstitution the final concentration of parecoxib is 20 mg/ml.

**Other ingredients are** dibasic sodium phosphate heptahydrate; phosphoric acid and/or sodium hydroxide may have been added for pH adjustment.

**Marketing authorisation holder**: Pharmacia Europe EEIG, Sandwich, Kent CT13 9NJ, United Kingdom.

**Manufacturer**: Pharmacia Limited, Whalton Road, Morpeth, Northumberland NE61 3YA, United Kingdom.

## 1. WHAT Dynastat IS AND WHAT IT'S USED FOR

Dynastat is a powder for solution for injection. It is supplied in cartons containing 10 glass vials.

**Dynastat is used to treat pain**. The injection is given to you by a doctor or nurse, usually in a hospital or clinic, such as 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. There are other prostaglandins that protect the stomach lining or cause the blood to clot, and Dynastat does not affect those.

## 2. BEFORE YOU ARE GIVEN Dynastat

**You will not be given Dynastat…**
- if you are hypersensitive (allergic) to parecoxib or any of the other ingredients of Dynastat
- if you have had an allergic reaction to a group of medicines called "sulphonamides" (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- 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 breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn's disease)
- if you have severe heart failure
- **if you are about to have heart surgery**

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

**Taking special care with Dynastat**
Some people will need special care from their doctors when they are given Dynastat.
**Make sure your doctor knows**, before you are given Dynastat …
- **If you have had an ulcer, bleeding or perforation of the gastrointestinal tract**
- **If you are taking acetylsalicylic acid or other NSAIDs** (e.g. ibuprofen)
- **If you have heart failure, ischaemic heart disease, peripheral vascular disease, high blood pressure, or if you have had a stroke**
- **If you are taking anti-platelet therapies** (e.g. acetylsalicylic acid)
- **If you have fluid retention** *(oedema)*
- **If you have liver or kidney disease**
- **If you might be 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)
- **If you are a woman trying to become pregnant**

**Pregnant or breast-feeding women**
- **If you are pregnant**, tell your doctor, as Dynastat may not be right for you. You will not be given Dynastat in the last three months of pregnancy.
- **If you are breast-feeding**, you must not have Dynastat. Ask your doctor for advice: it may be better to stop breast-feeding altogether to take the injections.

Get advice from a doctor or pharmacist before taking any medicine if you're pregnant or breast-feeding.

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

**Other medicines and Dynastat**
**Tell your doctor or nurse about any other medicines** you are taking or took recently (in the last week) – even medicines you bought yourself without a prescription. 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 or other anti-inflammatory drugs
- Fluconazole – used for fungal infections
- ACE inhibitors – used for high blood pressure and heart conditions
- Cyclosporin or Tacrolimus – used after transplants
- Warfarin – or other medicines used to prevent blood clots
- Lithium – used to treat depression.
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Theophylline – used for asthma
- Methotrexate – used for rheumatoid arthritis and cancer
- Antidepressants – used to treat depression
- Neuroleptics – used to treat psychoses

Dynastat can be used in combination with low dose acetylsalicylic acid

## 3. HOW THE INJECTION IS GIVEN

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. You will only be given Dynastat for short periods, and only for pain relief.

**If there are particles** in the injection solution or if either the powder or solution is discoloured, the product will not be used.

**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
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

**Children and adolescents under the age of 18 will not be given** Dynastat. People aged 18 and over will be given the adult dose.

## 4. POSSIBLE SIDE EFFECTS

Some people given Dynastat can have side effects. If you notice any of these, or any other effects of the injections not mentioned, **tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.**

**More common effects**
***These could affect between 1 and 10 in every 100 people***
- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual
- Dry socket (inflammation and pain after a tooth extraction)

**> If any of these affects you, talk to your doctor or nurse.**

**Uncommon effects**
***These could affect less than 1 in every 100 people***
- Worsening of high blood pressure
- Ulcers in the digestive system
- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.

**> If any of these affects you, talk to your doctor or nurse**.

**Rare Effects**
***These could affect less than 1 in every 1000 people.***

- **Rash or ulceration in any part of your body (e.g. skin, mouth, eyes, face, lips or tongue), or any other signs of allergic** reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin
- **The onset of these events can occur at any time but most often occur in the first 2 weeks of treatment; the reported rate of these events appears to be greater for valdecoxib as compared to other cox-2 inhibitors**
- Acute kidney failure.
- Heart failure, heart attack
- Hepatitis (inflamed liver)

**> If any of these affects you, tell your doctor or nurse immediately**.

## 5. STORING Dynastat

**For Section 5**
please turn over >

There are no special storage instructions.

Keep out of the reach or sight of children.

The product should not be used after the expiry date stated on the label.

Your doctor will use Dynastat as soon as possible after it is mixed with solvent.
**If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.

## 6. OTHER INFORMATION

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 approved on {date}**

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## 7. INFORMATION FOR THE HEALTH PROFESSIONAL

**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.

**Reconstitution solvents**

**This medicinal product must not be mixed** with other medicinal products and is to be reconstituted only with:

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

Use of Ringer-Lactate solution for injection or glucose 50 g/l (5%) in Ringer-Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is **not** recommended. Use of Sterile Water for Injection for reconsitution is not recommended, as the resulting solution is **not** isotonic.

**Reconstitution process**

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

*20 mg vial*: Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the parecoxib 20 mg vial. Withdraw with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 20 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.**

**IV line solution compatibility**

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

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

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

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

**The solution is for single use only and must not be stored in a refrigerator or freezer.**