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Bextra (valdecoxib) tablets

IMPORTANT NEW SAFETY INFORMATION
CARDIOVASCULAR RISK

21st February 2005

Dear Healthcare Professional,

In December 2004, you received safety information about Bextra (valdecoxib) regarding the contraindication in Coronary Artery Bypass Graft Surgery and additional information on severe adverse skin reactions. On February 17th 2005 Pfizer, following a discussion with the European Medicines Agency (EMEA) has revised the product labelling with important new Bextra safety information.

Summary of the prescribing information and changes are outlined below:

Bextra is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and primary dysmenorrhoea.

- In osteoarthritis and rheumatoid arthritis: the recommended daily dose is 10 mg taken once daily. Some patients may receive additional benefit from 20 mg once daily. In the absence of increased therapeutic benefit after two weeks, other therapeutic options should be considered.
- For 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.
- In all cases the patient's response to therapy should be re-evaluated periodically. The decision to prescribe Bextra should be based on an assessment of the individual patient's overall risk. Cardiovascular risks of treatment may increase with dose and duration of exposure, therefore the lowest effective daily dose should be used for the shortest duration possible.

Bextra is now CONTRAINDICATED in patients with established ischaemic heart disease **and/or cerebrovascular disease.** In addition Bextra is now contraindicated in class II-IV NYHA congestive heart failure. Bextra should also not be used in the treatment of post-operative pain following coronary artery bypass graft (CABG) surgery. **Bextra should not be prescribed to such patients.**

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

Physicians are advised to consider this new information when making the decision to prescribe Bextra.

The Product Information for Bextra has now been revised accordingly (see attached).

If you have any questions concerning this important safety information, please contact Pfizer Ltd. on freephone 1800 633 363 and ask for Medical Information.

Any suspected adverse drug reactions should be notified to the drug safety group at Pfizer Ltd., UK and the Irish Medicines Board in the usual away. The contact details for Pfizer are Pfizer Ltd., Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK or by using freephone 1800 633 363 and asking for the Drug Safety Group.

Yours Sincerely,

John Farrell.

.....
Dr John Farrell
Medical Director

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets
Bextra 20 mg film-coated tablets
Bextra 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bextra 10 mg: Each film-coated tablet contains 10 mg valdecoxib.

Bextra 20 mg: Each film-coated tablet contains 20 mg valdecoxib.

Bextra 40 mg: Each film-coated tablet contains 40 mg valdecoxib.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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

Bextra 20 mg: White, capsule-shaped, debossed '20' on one side and '7815' on the other.

Bextra 40 mg: Yellow, heptagon-shaped, debossed '40' 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.

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

4.2 Posology and method of administration

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

As the cardiovascular risks of valdecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (4.3, 4.4).

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. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

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.

Congestive heart failure (NYHA II-IV).

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

Established ischaemic heart disease and/or cerebrovascular disease.

4.4 Special warnings and special precautions for use

As the cardiovascular risks of valdecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (4.2, 4.3).

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

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 status in these patients (see section 5.1).

Valdecoxib has not been studied in cardiovascular revascularization procedures other than coronary artery bypass graft procedures. Studies in other surgeries than CABG procedures included patients with ASA (American Society of Anaesthesiology) Physical Status Class I-III only.

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

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with 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 further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when valdecoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs.* NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).

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).

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

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 complications. Cardiovascular/thromboembolic events include myocardial infarction, stroke/TIA, pulmonary embolus and deep vein thrombosis (see section 4.3 and 5.1).

In post-marketing experience, the following 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.

Bextra 10 mg and 20mg:
The film-coat contains titanium dioxide (E171), hypromellose (E464), macrogol 400, polysorbate 80 (E433).

Bextra 40 mg:
The film-coat contains titanium dioxide (E171), hypromellose (E464), macrogol 400, polysorbate 80 (E433), iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bextra 10 mg and 20 mg:
3 years.

Bextra 40 mg:
2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Bextra 10mg and 20 mg:

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.

Bextra 40 mg:

2 tablets
5 tablets
PVC/aluminium foil blisters

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)

Bextra 10 mg:

EU/1/02/239/001
EU/1/02/239/002

EU/1/02/239/003
EU/1/02/239/004
EU/1/02/239/005
EU/1/02/239/006
EU/1/02/239/007
EU/1/02/239/008
EU/1/02/239/009
EU/1/02/239/010
EU/1/02/239/025
EU/1/02/239/026

Bextra 20 mg:

EU/1/02/239/011
EU/1/02/239/012
EU/1/02/239/013
EU/1/02/239/014
EU/1/02/239/015
EU/1/02/239/016
EU/1/02/239/017
EU/1/02/239/018
EU/1/02/239/019
EU/1/02/239/020
EU/1/02/239/027
EU/1/02/239/028

Bextra 40 mg:

EU/1/02/239/021
EU/1/02/239/022
EU/1/02/239/023
EU/1/02/239/024
EU/1/02/239/029
EU/1/02/239/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27th March 2003

10. DATE OF REVISION OF THE TEXT

17th February 2005