ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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).

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.

Following coronary artery bypass graft surgery, caution should be observed when administering valdecoxib as these patients may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m^2 (see section 4.8).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib (see section 4.8).Valdecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see section 4.3).

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 80 mg/day may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

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, 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.

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

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg valdecoxib.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, capsule-shaped, debossed '20' 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).

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.

Following coronary artery bypass graft surgery, caution should be observed when administering valdecoxib as these patients may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m^2 (see section 4.8).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib (see section 4.8).Valdecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see section 4.3).

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 80 mg/day may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

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, 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.

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/1/02/239/011-020, 27-28

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 March 2003

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg valdecoxib.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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.

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).

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.

Following coronary artery bypass graft surgery, caution should be observed when administering valdecoxib as these patients may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m^2 (see section 4.8).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib (see section 4.8).Valdecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see section 4.3).

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 80 mg/day may have a higher risk of adverse reactions, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

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, 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.

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), iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

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)

EU/1/02/239/021-024, 29-30

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 March 2003

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pharmacia Ltd
Whalton Road
Morpeth
Northumberland
NE61 3YA
United Kingdom

Heinrich Mack Nachf GmbH & Co KG
Heinrich-Mack Strasse 35
DE-89257 Illertissen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/025

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/001

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/002

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/003

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/004

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

50 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/005

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/006

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

20 x 1 tablets (part of multipack)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/026

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/007

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/008

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 (5 packs of 20 x 1) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/026

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

300 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/009

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/010

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Unit dose and non-unit dose foil for 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 10 mg tablets

Valdecoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 10 mg film-coated tablets

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

Bextra 10 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 tablets
Each tablet contains 10 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/009

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 10 mg film-coated tablets

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

Bextra 10 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 tablets
Each tablet contains 10 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/010

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/027

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/011

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/012

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/013

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/014

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

50 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/015

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/016

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

20 x 1 tablets (part of multipack)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/028

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/017

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/018

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 (5 packs of 20 x 1) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/028

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

300 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/019

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/020

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Unit dose and non-unit dose foil for 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 20 mg tablets

Valdecoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 20 mg film-coated tablets

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

Bextra 20 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 tablets
Each tablet contains 20 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/019

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 20 mg film-coated tablets

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

Bextra 20 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 tablets
Each tablet contains 20 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/020

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/021

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for blister pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/022

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

20 x 1 tablets (part of multipack)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/030

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/029

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for unit dose blister pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

100 x 1 (5 packs of 20 x 1) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/030

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

300 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/023

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton for bottle pack: 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg film-coated tablets

Valdecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg valdecoxib

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate – see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/239/024

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read enclosed leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Unit dose and non-unit dose foil for 40 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Bextra 40 mg tablets

Valdecoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmacia-Pfizer EEIG

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 40 mg film-coated tablets

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

Bextra 40 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 tablets
Each tablet contains 40 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/023

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 40 mg film-coated tablets

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

Bextra 40 mg film-coated tablets

Valdecoxib

For oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 tablets
Each tablet contains 40 mg valdecoxib

Medicinal product subject to medical prescription.
Keep out of reach and sight of children.
Read enclosed leaflet before use.

Pharmacia-Pfizer EEIG
Sandwich
Kent
CT13 9NJ
United Kingdom

EU/1/02/239/024

B. PACKAGE LEAFLET

PACKAGE LEAFLET

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

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

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 are about to have heart surgery and have had a stroke
- 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 have 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
- 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 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)
- 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

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PACKAGE LEAFLET

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- 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 20 mg film-coated tablets
Valdecoxib
The active substance in Bextra is valdecoxib.
Bextra film-coated tablets contain 20 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:
Pharmacia Limited, Whalton Road, Morpeth, Northumberland NE61 3YA, United Kingdom

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 20 mg film-coated tablets are white, capsule-shaped and are marked with '20' 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

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 are about to have heart surgery and have had a stroke
- 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 have 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
- 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 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)
- 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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- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
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What's in this leaflet:

Bextra 40 mg film-coated tablets
Valdecoxib
The active substance in Bextra is valdecoxib.
Bextra film-coated tablets contain 40 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), iron oxide yellow (E172).

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

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

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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 40 mg film-coated tablets are yellow, heptagon-shaped and are marked with '40' on one side and '7815' on the other side.

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

Blister packs of: 2 and 5 film-coated tablets
Unit dose blister packs of: 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 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

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 are about to have heart surgery and have had a stroke
- 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 have 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
- 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 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)
- 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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