SCIENTIFIC DISCUSSION

Name of the medicinal product:	Dynastat
Applicant:	Pharmacia Europe EEIG. Hillbottom Road High Wycombe Buckinghamshire HP12 4PX United Kingdom
Active substance:	Parecoxib sodium
International Non-proprietary Name:	Parecoxib
Pharmaco-therapeutic group (ATC Code):	Coxibs M01AH04
Therapeutic indications:	For the short-term treatment of postoperative pain

1. Introduction

Acute pain is commonly associated with tissue damage caused by injury or surgery. Parenteral treatments are usually preferred when acute pain conditions are moderately severe or worse, and are required in acute pain when oral (or rectal) administration is inappropriate e.g. postoperatively.

The cornerstones of analgesia in acute pain continue to be opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and regional/local anaesthesia/analgesia techniques. In the postoperative setting these therapies are often employed as a multi-modal analgesia.

From the early 1970s it was known that aspirin and other NSAIDs acted by inhibiting cyclooxygenase (COX). COX is the enzyme involved in the formation of thromboxane and the prostaglandins (often pro-inflammatory substances) from arachidonic acid.

It was thought for many years, that COX was a single enzyme. However, basic research into prostaglandin metabolism using cultured cell lines gradually led to the realisation that the COX generated by mitogen stimulation was a variant of that already known. The protein structure and cDNA of induced COX was different to that of constitutively expressed COX. The two proteins are now known as COX-1 (constitutive) and COX-2 (induced). Further work revealed that, in very general terms, COX-1 could be said to have a tissue homeostatic function, and COX-2 an inflammatory function. Therefore, it was thought that if an NSAID could be developed which selectively inhibited COX-2, it might retain the valuable anti-inflammatory properties and lose the tissue damaging effects of non-selective NSAIDS.

Parecoxib sodium is a water-soluble sodium salt of the amide prodrug of valdecoxib. Parecoxib undergoes enzymatic hydrolysis in vivo to the active moiety valdecoxib, and is formulated as a powder for solution for parenteral administration. Valdecoxib is a selective inhibitor of the enzyme COX-2.

The Marketing Authorisation Application has been evaluated for parecoxib sodium under the trade names Dynastat for the indication "for the short-term treatment of postoperative pain".

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Dynastat is formulated as a freeze-dried powder for solution for injection in glass vials containing either 20 mg or 40 mg of parecoxib (as the sodium salt). When reconstituted with 0.9 % w/v of sterile sodium chloride solution (1 ml for the 20 mg presentation and 2 ml for the 40 mg presentation), the same final concentration for administration of 20 mg/ml is obtained from both vial sizes. The product is to be available in packs both with and without ampoules (1 ml and 2 ml contents) of solvent [9 mg/ml (0.9%) sodium chloride solution] for reconstitution.

Active substance

Parecoxib sodium is a water-soluble pro-drug of valdecoxib which is a poorly water-soluble COX-2 inhibitor. Valdecoxib is also the major degradant from thermal-, solution- or light-stressed degradation.

The structure has been confirmed by single crystal X-ray analysis of the free acid (parecoxib), by elemental analysis and by NMR of parecoxib sodium. Other techniques used for structure elucidation included, IR, MS and UV.

Parecoxib has no asymmetric centres. Several anhydrous and solvated crystal forms have been shown to exist (by powder X-ray diffraction and thermal analysis), but it has been demonstrated that during the product manufacturing process that the anhydrous and non-solvated Form I of parecoxib sodium is formed. Details of the reference standard and its characterisation are adequate.

The active substance is synthesised in a five-step process which is fully described and adequately controlled. The specifications for the starting materials, the isolated intermediate (valdecoxib), and the solvents and reagents are adequate. The first three steps of the synthesis produce valdecoxib, and the last two steps form parecoxib sodium. Although earlier processes have been used for pre-clinical

and clinical testing, but no new impurities which need to be further qualified in toxicity studies arise from the current process.

The potential impurities from the synthesis are discussed. Only four impurities have been detected.

The specification for parecoxib sodium contains suitable tests for identity, assay (by a stability indicating HPLC method), impurities (a single specified impurity and any single unspecified impurity and total impurities), residual organic solvents, bacterial endotoxins and other general purity tests. The limits for impurities are toxicologically acceptable.

Batch analyses results, including results from production scale batches, demonstrate satisfactory uniformity and compliance with the specification.

Stability

The active substance is stored in polyethylene bags inside aluminium foil laminate bags. Stability data are available for 104 weeks storage at long-term ICH conditions and 26 weeks at intermediate and accelerated conditions. Results are within specification, there is no degradation and no trends are apparent. A re-test period of two years is claimed (at 25°C) and is supported by the data provided. The stability of the first three full-scale production batches of the active substance made post-approval by the proposed site (Pharmacia Limited, Morpeth, UK) will be monitored and the results forwarded when available.

Stress studies on a solution of parecoxib sodium demonstrate that stability increases with increasing pH and reaches a plateau between pH 7 to pH 9. Degradation increases with temperature.

Other ingredients

All the excipients are controlled to the relevant Ph Eur or USP standards. None of the ingredients are derived from animal sources.

The vials are made of colourless glass which comply with the PhEur requirements for Type I glass. For the 20 mg dose the vial size is 2 ml, and for the 40 mg dose the vial size is 5 ml. The butyl rubber stoppers have a fluorocarbon lamination on the product surface, a silicone coating on non-product surfaces and comply with the PhEur requirements for rubber closures for aqueous preparations for parenteral use. The colour of the flip-off cap on the aluminium overseals (for which specifications have been provided) is yellow for the 20 mg dose and purple for the 40 mg dose. Cardboard cartons (or equivalent) are used as secondary packaging.

The ampoules of solvent [9 mg/ml (0.9%) sodium chloride solution] contain sodium chloride Ph Eur and water for injections Ph Eur, and if necessary for pH adjustment, hydrochloric acid and/or sodium hydroxide Ph Eur. The ampoules are 2 ml size, but may have a 1 ml or 2 ml fill volume. They are made of colourless glass and comply with the Ph Eur requirements for Type I glass.

Product development and finished product

Due to the poor aqueous solubility of the main degradation product, valdecoxib, the pivotal aim of the pharmaceutical development was to produce a stable formulation where the formation of valdecoxib was minimised. Experiments on autoclaving vials of 20 mg/ml solution at 121 °C for 15 minutes resulted in the appearance of long crystals in the majority of the vials tested and this justified the development of a lyophilised product.

Different formulations containing buffer/bulking agent/solubiliser were tested for stability. The commercial composition, containing dibasic sodium phosphate heptahydrate as the only excipient, was the most stable formulation investigated. Moreover, this product reconstituted faster than the early formulation containing mannitol (which had been used in the Phase I/Phase II trials).

The aqueous solubility of parecoxib sodium at 20°C is 18 mg/ml at pH 7.8 but 220 mg/ml at pH 8.3. The pH specification for the product after dilution (with sodium chloride solution) is 7.5 – 8.5. The solubility of parecoxib sodium at pH values >7.5 is greater than predicted by ionisation, and is attributed to the formation of self-association complexes (micelles) (CMC = 20 mg/ml).

Reconstituted solutions are hypotonic, hence the use of 9 mg/ml (0.9 %) sodium chloride as a reconstitution solution which renders the injection almost isotonic.

The commercial formulation consists of parecoxib sodium (active substance), dibasic sodium phosphate (buffering agent), phosphoric acid and sodium hydroxide (if needed for pH adjustment), and water for injections (vehicle removed during lyophilisation) and nitrogen (inert headspace gas).

Physical, chemical and microbiological stability data are provided to support the instructions for administration given in section 6.6 of the SPC.

Chemical and physical stability after 48 hours was demonstrated after dilution with 9 mg/ml (0.9%) sodium chloride solution, 50 g/L (5%) glucose solution for infusion and 4.5 mg/ml (0.45%) sodium chloride and 50 g/L (5%) glucose solution for injection. Y-site compatibility was also investigated. For Ringer Lactate solution for injection, which cannot be used as a diluent because of the formation of crystals after 8 hours, studies showed that the reconstituted product can be injected into a line delivering this solution without precipitation. The reconstituted product has some inherent antimicrobial properties.

Manufacture

The manufacturing process, including the in-process controls (IPCs), has been well documented (including a flow chart). After dissolution and mixing of all the ingredients, the solution is sterilised by filtration (two 0.22μm filters), aseptically filled into sterilised vials (partially stoppered with sterilised butyl rubber stoppers) and then lyophilised.

Appropriate IPCs limits are set for pH, assay and fill weight. Although the limit for bioburden of NMT 10 CFU/ml limit is above that specified in the guidelines (10 CFU/100 ml), the proposed limit has been justified and it has been demonstrated that the manufacture reduces the bioburden to within the guideline limit.

The manufacturing process has been adequately validated at all three proposed manufacturing sites.

The ampoules of solvent [9mg/ml (0.9%) sodium chloride solution] are manufactured at two sites by a conventional solution process. Full details of the manufacture, filling and sealing of the ampoules and then terminal autoclaving under standard conditions are provided. The processes have been satisfactorily validated.

Product specification

The finished product release specification contains suitable tests for a parenteral powder for solution for injection. Identity is assured by IR, and content uniformity by UV and content and degradants are controlled using a stability indicating HPLC assay. . The limits for individual (NMT 0.2% for a single specified impurity and NMT 0.2% for any other single unspecified) and total (NMT 0.5%) degradants are acceptable. Water is controlled as the product is hygroscopic. Standard PhEur tests are included - for clarity, opalescence, particulate contamination, sterility and bacterial endotoxins. The finished product specification also includes tests and limits for pH and reconstitution time.

The shelf-life specification differs in that it has a higher limit for water content (NMT 5.0%), a higher limit (NMT 0.5%) for the major degradation product, valdecoxib, and also a higher limit (NMT 0.8%) for total impurities.

The HPLC method for assay and degradation products, and the UV method for content uniformity have been satisfactorily validated.

Batch analyses results for 43 batches including production-scale batches, manufactured at Searle in Skokie, Searle in Barceloneta, Dr.Madaus and Ben Venue Laboratories, USA were presented. The results comply with the agreed specifications and demonstrate satisfactory uniformity.

The ampoules of solvent [9 mg/ml (0.9%) sodium chloride solution] are tested according to the BP monograph for "Sodium chloride intravenous infusion". Results from batch analyses data (both fill volume sizes) are provided and demonstrate the batches meet the specification and also that there is consistency of manufacture.

Stability of the Product

Satisfactory stability data are available after 104 weeks long-term, 52 weeks intermediate and 26 weeks accelerated storage (ICH conditions) on three batches of each vial size (20 mg and 40 mg) made by two manufacturing sites. Stability results comply with the shelf-life specification and there was no trend in content results. Slight increases in the levels of both valdecoxib (the only degradant seen above 0.1%) and water content were seen with time.

The product was also tested under stress conditions. Photostability testing showed that the product without secondary packaging is slightly sensitive to light, although it remained within specifications when exposed to standard ICH testing conditions. Thermal degradation studies demonstrated the stability of the product to heat, as after 27 weeks at 70°C the level of valdecoxib (the only degradant observed) was only 0.58%.

The stability data provide support the three year shelf-life and demonstrate there is no need for any storage recommendations for the product, either with regard to temperature or light.

Investigations on stability of the **reconstituted** product show that the product reconstituted with either the 9 mg/ml (0.9%) sodium chloride solution, 50 g/L (5%) glucose solution for infusion 4.5 mg/ml (0.45%) sodium chloride and 50 g/L (5%) glucose solution for injection is physically and chemically stable for 48 hours at 25°C. The sodium chloride diluted product was also tested after storage in polypropylene syringes and glass syringes. The use of saline solutions at both the upper and lower release pH limits (4.5 and 7.0) were investigated as well as dextrose solutions at a low pH (3.5), but no crystallisation was evident. The recommended shelf-life after reconstitution is 12 hours at 25°C, and this has therefore been supported by physical and chemical stability data.

There are three conditions under which parecoxib has been observed to crystallise out of the reconstituted injection and these are refrigeration, use of acidic diluents which result in an initial pH of 7.2 or less, and storage of a solution reconstituted with an acidic diluent which results in an initial pH of 7.4 or less. There are therefore additional warnings in the product information not to refrigerate or freeze the reconstituted product and these are fully justified.

The stability data provided for the ampoules of solvent [9mg/ml (0.9%) sodium chloride solution] support the three year shelf-life and demonstrate there is no need for any special storage recommendations.

The stability results justify the claimed shelf-lives (before and after reconstitution) as defined in the SPC.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

- *In vitro* studies and *in vivo* studies

The pharmacological activity of parecoxib is exerted primarily via it's principle metabolite valdecoxib, but also by an active metabolite of valdecoxib (M1), which represents about 10% of the concentration of valdecoxib. These have been shown, *in vitro* and *in vivo*, to exhibit COX-2 inhibition at considerably lower concentrations than COX-1 inhibition.

Anti-inflammatory, analgesic and anti-pyretic activity were demonstrated in a number of animal models.

Parecoxib and valdecoxib showed varying degrees of potency in the carrageenan-induced inflamed paw model, adjuvant-induced arthritis model and models of surgically-induced pain.

The anti-pyretic activity of parecoxib and valdecoxib was assessed in a canine model of fever induced with bacterial endotoxin or lipopolysaccharide (LPS); both parecoxib and valdecoxib reduced fever.

- General and safety pharmacology programme

No adverse cardiovascular effects were seen. No disturbances of ECGs, including QT interval assessment, or adverse change in cardiovascular function were observed in conscious dogs. Plasma concentrations of parecoxib, valdecoxib and M1 in dogs were 3-, 19- and 124-fold greater, respectively, than anticipated with the maximum recommended human dose (MRHD).Urethane anaesthetised guinea pigs were exposed to plasma concentrations of parecoxib, valdecoxib and M1 which were less than, equal to and 11-fold greater, respectively, than those achieved with the MRHD.

In both animal models minor cardiovascular changes, and in guinea pigs pulmonary changes, were seen. The changes were transient and not related to dose and were thus not considered to be toxicologically significant.

Doses of parecoxib used in neurobehavioural tests were too low to assess possible effects. Diminished renal function and delayed healing of bacterial infections were seen at higher doses.

Valdecoxib and M1 showed no interactions with receptors or enzymes of potential clinical significance.

- Pharmacodynamic drug interactions

No formal drug-drug interaction studies have been conducted in animals.

Pharmacokinetics

The absorption and distribution of parecoxib following i.v. administration was rapid and widespread. Parecoxib is rapidly converted to valdecoxib with first order kinetics. Bioavailability of valdecoxib and M1 is high following parecoxib administration in all species but the rabbit. Maximum human exposure has been calculated based on the available data, resulting in 2-fold and 0.8-fold safety margins for parecoxib and valdecoxib, respectively, in the repeated dose rat and dog studies.

Protein binding is high for parecoxib, valdecoxib and M1. The majority of tissue concentrations were equivalent to that of plasma, including amniotic fluid, milk and pigmented tissues. There was no evidence of accumulation of the parent drug or metabolites. Metabolism is rapid and complex; over 15 metabolites have been identified. All but one (minor) human metabolite have been seen in at least one of the animal species tested.

Parecoxib is converted to valdecoxib and propionic acid *in viv*o. At physiological pH propionic acid exists as propionate, a precursor for gluconeogenesis. In Europe, propionic acid is approved as a preservative (mould inhibitor) for human grains/grain products and also as a food additive.

Species differences in the metabolism of parecoxib and valdecoxib were observed. Collectively, the species used for toxicological assessment of parecoxib form all of the metabolites found in humans with the exception of the valdecoxib N-glucuronide metabolite.

In vitro studies showed that both parecoxib and valdecoxib had a weak inhibitory potential for CYP2C9 and CYP2C19, but not for CYP3A4 or CYP2D9. The possible clinical relevance for these *in vitro* data are discussed in the clinical section.

Elimination is primarily faecal in the dog, but in the rat renal, biliary and faecal excretion appear to play equal roles.

Toxicology

- *Single dose toxicity*

In the acute rat study, 2 deaths were noted after a single dose of 45 mg/kg iv and 13 deaths at $\geq$150 mg/kg iv. 2/2 and 6/13 deaths occurred either immediately after dosing or after the 5-min toxicokinetic blood collection, the remaining 7/13 deaths occurred within 45 minutes of dosing. The lack of histo-pathological evidence is common to all 15 deaths on Day 1. Therefore, the NOEL is set at <45 mg/kg iv.

In the acute dog study, some clinical pathology parameters were observed in the 80mg/kg treatment group. These included an increase in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bile acids and white blood cell count. No changes were observed in platelet function or coagulation parameters.

- *Repeat dose toxicity*

In repeated dose studies, rats and dogs could only be maintained on low multiples of human therapeutic exposure levels because of dose-limiting toxic effects at sites typically susceptible to COX-inhibition (the GIT and skin in particular).

The GIT injuries were the most serious and consisted of focal transmural inflammation and necrosis, particularly of the ileum and jejunum, which typically progressed to perforation and fatal peritonitis.

A variety of skin lesions, including inflammation due to bacterial infection, thickening of the injection site and cage sores were seen in dogs following iv administration. A significant increase in septic skin lesions and a notable failure to heal, resulting in some premature sacrifice, was seen in repeated dose dog studies. It would appear that the delay in healing is a consequence of COX-2 inhibition and is common to many COX-inhibitors, both COX-2 selective and non-selective, the degree of delay being proportional to the effectiveness of the drug.

The only renal effect seen in the repeated dose toxicity studies with parecoxib sodium was a modest decrease in urinary sodium excretion in rats. Since sodium excretion by the kidney is partially regulated by prostaglandins, this effect was not unexpected.

Changes at the injection site (peri-vascular fibrosis, chronic inflammation, focal necrosis and haemorrhage) occurred with greater frequency in treated rats than in concurrent controls and were not fully reversible during the recovery period. Slight-significant decreases in erythroid parameters (RBC, Hct and Hgb concentration), total protein and serum albumin were considered to be due to the loss of blood from injured intestinal mucosa. The NOEL in rats was assigned in males and females as 25 and 12.5 mg/kg/day iv for 2-weeks or 10 and 2.5 mg/kg/day iv, in two equal doses, for 4-weeks. The NOAEL in rats was assigned in males and females as 25 and 10 mg/kg/day iv, in two equal doses, for 4-weeks. In dogs of both sexes a dose of 6 mg/kg/day iv, in two equal doses, was assigned as the NOAEL over 2-weeks dosing NOEL over 4-weeks dosing.

The data on Cmax and AUC in animals have been summarised and compared to human data following a 40 mg dose. The data suggests that for the multiple dose general toxicity studies in the rat there is an exposure factor of about 7 for Cmax and 11 for AUC for parecoxib, with slightly lower figures for valdecoxib, and much higher for M1. The ratios tend to be somewhat lower in females. For the dog there is an exposure ratio of 4 for Cmax and 11 for AUC for parecoxib. For valdecoxib the ratio is lower approximately 3 for Cmax and AUC, for M1 the ratio was approximately 30 for AUC and Cmax.

- *Genotoxicity*

A full series of genotoxicity studies has been conducted. The drug or its metabolites did not produce mutagenic effects in the Ames and the CHO/HGPRT assays. Chromosomal aberrations were produced by parecoxib at 4-hour incubation of CHO cells with and without the addition of S9 (rat liver microsomal preparations), but not at 24 hour incubation without the addition of S9. No effects were observed for the metabolites tested, thus the clastogenic effect seem to be associated with parecoxib itself. The clastogenic effect of parecoxib was not seen in the *in vivo* rat bone marrow micronucleus assay. Taken together, the data suggest that the results for chromosomal defects are equivocal and the safety margin based on the AUC implies low genotoxic risk for humans.

- *Carcinogenicity*

Carcinogenicity studies were not conducted, since parecoxib is intended for short-term use only.

- *Reproduction toxicity*

In the rat fertility study a reduction in gravid uterine weight was seen and was correlated with an increased post-implantation loss and reduced number of foetuses. In the developmental toxicity studies, the test substance clearly has the ability to increase post-implantation losses and resorptions in the rat and rabbit, in the absence of measurable maternal toxicity in the rabbit. In addition, there were several indications of developmental toxicity, including a possibly treatment-related increased incidence of skeletal malformations in rabbit foetuses, again in the absence of maternal toxicity. The overall development NOEL (No Observed Effect Level) in the rat was observed to be 12.5mg/kg/day based on reduced foetal weight and possible treatment-related increase in rudimentary 14^{th} rib. The NOEL for developmental toxicity for the rabbit was 20mg/kg/day based on increased post-implantation losses.

Adverse reproductive effects could be expected to result from drugs producing prostaglandin inhibition. Drugs of this class, including parecoxib, are not recommended in women attempting to conceive, and are contraindicated in the last trimester of pregnancy due to harmful pharmacological effects on pregnancy and/or the foetus/newborn child (i.e. uterina inertia and/or premature closure of the ductus arteriosus).

However, since parecoxib caused reproductive toxicity in animals at doses not producing maternal toxicity, the drug should be characterised as embryotoxic and thus should not be used in the first two trimesters of pregnancy or labour unless the benefit to the patient outweighs the potential risk to the foetus. The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and post-natal period. The drug is excreted in rat milk and should not be administered during lactation.

- *Local Tolerance*

Clinically relevant formulations of parecoxib produced slight-moderate irritation at im injection sites and no significant effect at iv injection sites in rabbits. However, the irritation seen at some injection sites in some of the repeat dose studies in rats and dogs suggests that there may in fact be some potential for irritation after iv administration.

The results of the two guinea pig studies (Magnusson and Kligman maximization assay) suggest that parecoxib is not likely to be a dermal sensitizer.

- *Environmental Risk Assessment*

Given the nature and proposed use of parecoxib, it is considered unlikely to have an adverse environmental impact. Parecoxib does not contain nor is it derived from genetically modified organisms (GMOs).

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

- Mechanism of action

Parecoxib and its active metabolite valdecoxib belong to the diarylheterocyclic family of cyclo-oxygenase (COX) inhibitors. Evidence of COX-2 selectivity comes principally from a study that used a transfected cell line to express recombinant COX-1 or COX-2. Cell homogenates were incubated in the presence of exogenous arachadonic acid and test drug. Using this assay, valdecoxib was approximately 28 000 fold more selective toward COX-2 compared to COX-1.

Dynamic studies:

In two clinical trials healthy young subjects with endoscopically normal gastric and duodenal mucosa underwent seven days treatment with parecoxib. In study 011 the 5% of patients in the placebo and parecoxib 20 mg/day groups were found to have a gastroduodenal ulcer or erosion. The mean score for any endoscopic abnormality was 0.27 for placebo, 0.43 for parecoxib 4.61 for ketorolac and 3.22 for naproxen. Erosions and ulcers were approximately ten fold higher for ketoralac and naproxen than for placebo. In study 030 the placebo rate for erosion or ulcer was 6%; that for parecoxib was 21% and that for ketorolac was 90%. The respective endoscopy scores were 0.22; 0.31; 0.97

Two similar studies were conducted in healthy elderly subjects the first study showed similar results to the healthy young subject studies and. the other one was discontinued because of the high incidence of ulceration in the ketorolac and naproxen treatment groups.

Effects on platelet function were investigated in three studies in healthy volunteers, including the elderly. Induced platelet aggregation using arachonidate, collagen and ADP, was significantly more affected in subjects receiving ketorolac than in those receiving parecoxib sodium, which differed little from placebo.

Renal effects based on measurements of urinary prostaglandins and fractional sodium secretion did not suggest any benefit of parecoxib sodium compared to ketorolac.

Pharmacokinetics

- General:

Absorption and dose linearity

In healthy male volunteers the pharmacokinetics of parecoxib/valdecoxib were compared following administration of 20 mg doses intravenously and by mouth. The kinetics after repeated intravenous administration for up to nine days were similar to those after single doses.

Distribution

Valdecoxib is about 95% protein bound over three orders of magnitude concentration in all species tested (including man): parecoxib is 97% bound. The minor metabolite with activity (M1) is at least 80% protein bound. There is partitioning of drug between red blood cells (RBC) and plasma with a ratio of about 4:1. The apparent volume of distribution of parecoxib in animals was 0.4 l/Kg and in man 6.7 l following intravenous and 16 .5 l following intramuscular injection of 20 mg.

Metabolism

Parecoxib is rapidly metabolised to proprionic acid and valdecoxib by hepatic carboxyesterases and is not dependant on the NADPH or cytochrome P450 systems. Parecoxib is stable (not metabolised) in whole blood and plasma. Proprionic acid, which exists as priorionate at physiological pH, is an endogenous substance which feeds into gluconeogenesis. For valdecoxib, the main metabolic pathway involves the hydroxylation of the methyl group on the isoxazole ring to form the metabolite M1.

In vitro studies of the subsequent metabolism of valdecoxib show that the CYP isoenzymes are involved particularly CYP3A4 and also CYP2C9. With increasing drug concentrations there was evidence of saturation of CYP2D6 and CYP1A2 indicating an inhibition of these enzymes by metabolites of parecoxib. The data provided allow no more than a 'semi-quantitative' evaluation of the relative contribution of the various isoenzymes.

Elimination

Parecoxib is rapidly and extensively converted to valdecoxib; the elimination half-life of the former being about forty minutes, the latter about eight hours. Mass balance studies show that elimination is predominantly urinary, 65.3%, with 15.5% in faeces, primarily as metabolites.

- **Pharmacokinetics in special populations**

Hepatic impairment

In patients with mild, or moderate hepatic impairment, bioavailability of both the pro-drug and active form increased with degree of impairment and the plasma clearance decreased (Table 1). The SPC recommends that the dose be halved in patients with moderate hepatic impairment and the drug is contraindicated in patients with severe hepatic impairment.

Table 1 Group mean increase in drug exposure (following multiple doses) by degree of hepatic impairment.

	Parecoxib	Valdecoxib
Cmax	mild = 0 moderate = 35%	mild = 30% moderate = 144%
AUC	mild = 0 moderate = 85%	mild = 18% moderate = 138%

Renal impairment

A study in patients with renal impairment showed an increase (8% to 36%) in the AUC of valdecoxib following a single 20 mg dose of parecoxib. The increase in AUC was not tightly correlated to the degree of renal impairment. No changes in valdecoxib clearance were found even in severe renal impairment and dialysis, consistent with the extensive elimination of valdecoxib via hepatic metabolism. About 65 % of the dose is excreted in the urine as inactive metabolites.

The Elderly

Bioavailability of valdecoxib is greater in the elderly after repeat oral administration, with healthy elderly subjects having a reduced apparent oral clearance of valdecoxib resulting in an approximately 40% higher plasma exposure compared to healthy young subjects. When adjusted for body weight, plasma exposure was on average 16% higher in elderly females compared to elderly males.

As elderly female patients not uncommonly weigh less than 50 kg, a dose reduction in this group seems reasonable and has been included in the SPC.

- Interaction studies:

A number of interaction studies were conducted with the oral formulation, valdecoxib. Extrapolation from interaction studies done with valdecoxib to parecocib is valid since the conversion of parecoxib to valdecoxib is rapid and therefore the exposure to valdecoxib following parenteral parecoxib or oral valdecoxib is considered to be equivalent.

Valdecoxib displays a moderately high affinity to **CYP2D6**, and even though the inhibition of CYP2D6 by valdecoxib was not complete, it is reasonable to believe that inhibition of this isoenzyme is the principal interacting mechanism with dextromethorphan (CYP2D6 substrate). As several drugs and drug groups (e.g. codeine, antidepressants such as SSRIs, neuroleptics, and antiarrhythmics) are substrates for CYP2D6 caution should be observed when coadministering parecoxib with drugs that are predominantly metabolised by CYP 2D6

Plasma exposure to omeprazole (CYP2C19 substrate) was increased following administration with valdecoxib, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor. Reference should be made to the potential inhibition of substrates of **CYP2C19** (e.g. phenytoin, diazepam or imipramine) by valdecoxib.

Coadministration of valdecoxib with warfarin over 7 days resulted in a 10-12% increase in plasma exposure (AUC) of warfarin and a small increase (approximately 8%) in mean prothrombin time and mean International Normalized Ratio values. These small increases in the PT and INR values were not considered clinically important. However, the SPC recommends that anticoagulant therapy be monitored in patients receiving warfarin or similar agents due to potential increased risk of bleeding complications.

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

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

Enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administrated with e.g. carbamazepine, phenytoin, rifampicin or dexamethasone and the potential interactions of these drugs have been highlighted in the SPC.

The effect of parecoxib sodium/valdecoxib on the elimination of drugs where renal function plays a major role in elimination has been considered for medications such as methotrexate and lithium. Co-administration of parecoxib and methotrexate resulted in a reduced renal clearance, but plasma clearance of methotrexate was not affected.. A recommendation for the monitoring of lithium serum concentration and methotrexate-related toxicity has been included in the SPC.

Co-administration with heparin did not result in alteration of activated Partial Thromboplastin Time (aPTT). No differences were detected in group mean thromboplastin time (PT) or platelet counts.

Clinical efficacy

All clinical trials were performed according to GCP standards.

In the clinical trial programme conducted by the applicant (Table 2), the inclusion and exclusion criteria can be summarised as selecting adult patients (at least eighteen years old) who were in moderate to severe pain following the surgical procedure and did not have other serious concurrent illness. The requirement for the patient to be in pain is different in the studies of prophylaxis where treatments were started pre-operatively with the aim of avoiding pain.

Pain was measured using a variety of rating scores, perhaps the most useful of which is the Pain Intensity Difference (PID), which compares pain at a given time with that at baseline: it appears to provide an 'area under the curve'-type measure of pain relief with respect to time and is used in most of the studies. For primary end points pain intensity was assessed using a 4-point categorical rating scale. The pain intensity visual analog scale (VAS) was applied in some of the secondary end-points.

Table 2 Overview of analgesic efficacy studies

Model and Study Number	Study Category	Parecoxib sodium dose (mg)	[a]Comparator	No. Enrolled	Inclusion Criteria[b]
Post-Dental Surgery Analgesia					
003	Range finding	IM Single Dose: 1, 2, 5, 10, 20	P, K	353	Surgical extraction ipsilateral impacted third molars; Moderate pain (categorical) and VAS ≥50 mm within 6 hours after surgery
004	Range finding	IV Single Dose: 1, 2, 5, 10, 20, 50, 100	P, K	457	same as 003
014	Pivotal	Single Dose: 20 IV, 20 IM	P, V, I, K, T	351	same as 003
025	Pivotal	Single Dose IM and IV: 20, 40	P, K	304	same as 003
Post-Gynaecological Surgery Analgesia					
019	Pivotal	IV Single Dose: 20, 40	P, K, M	202	Elective abdominal hysterectomy/ myomectomy; Moderate incisional pain (categorical) and VAS ≥45 mm within 6 hours after discontinuation of patient controlled analgesia (PCA) within 24 hours of surgery
021[c]	Pivotal	IV Repeated Dose: 20, 40	P, K, M	208	same as 019
Post-Orthopaedic Surgery Analgesia					
018	Pivotal	IV Single Dose: 20, 40	P, K, M	208	Unilateral total knee arthroplasty under general anaesthesia; Moderate pain (categorical) and VAS ≥45 mm within 6 hours after discontinuation of PCA
020[c]	Pivotal	IV Repeated Dose: 20, 40	P, K, M	204	Unilateral total hip arthroplasty (initial or revision) under general anaesthesia; Moderate pain (categorical) and VAS ≥45 mm within 6 hours after discontinuation of PCA
Pre-Emptive/Preventative Analgesia-Dental and Orthopaedic Surgery					
022	Pivotal	IV Single Dose: 20, 40, 80	P	224	Surgical extraction ipsilateral impacted third molar teeth.
037	Pivotal	IV Single Dose: 20, 40	P	203	Orthopaedic surgery under general or local anaesthesia
v024	Supportive	V PO Single Dose: 10, 20, 40, 80	P	284	same as 022
v037	Supportive	V PO Single Dose: 20, 40, 80	P	223	Unilateral first metatarsal bunionectomy under regional anaesthesia
Opioid-Sparing[d]-CABG or Gynaecological Surgery					
035	Pivotal	IV Repeated Dose: 40 q 12 hours	P	462	CABG surgery
029	Pivotal	IV Repeated Dose: 20, 40 q 12 hours	P	216	Abdominal hysterectomy/ myomectomy

[a] P = placebo; K = ketorolac 30 mg IV (60 mg IM in 025, 15 mg IV in 020); I = ibuprofen 400 mg PO; V = valdecoxib PO; T = tramadol 100 mg PO; M = morphine sulphate 4 mg IV.
[b]TAH = total abdominal hysterectomy; VAS = visual analogue scale; PCA = patient-controlled analgesia; THA = total hip arthroplasty; CABG = coronary artery bypass graft.
[c]Studies with repeated-dose phases, study drug was administered BID for up to 5 days.
[d]Duration of parecoxib sodium IV administration in the Study 029 was 36 hours. In Study 035, parecoxib sodium 40 mg IV q 12 hours for 72 hours was followed by valdecoxib 40 mg PO every 12 hours for up to 14 days.

Main efficacy studies

- **Dental surgery**

Four studies were conducted in dental surgery in which parecoxib was administered post-operatively all involving patients undergoing extraction of one or more molar teeth. One study involved pre-operative administration of parecoxib.

In **study 003,** patients (50 or 51 per group) received a single intramuscular dose of: placebo, parecoxib 1 mg, 2 mg, 5 mg, 10 mg, 20 mg, ketorolac 30 mg. Doses of parecoxib above 10 mg gave satisfactory pain relief.

Study 004 was conducted to a similar design as 003 with two exceptions; the intravenous route was used instead of the intramuscular, and the two highest doses of parecoxib administered were 50 mg and 100 mg. Fifty-one patients received each dose of parecoxib and fifty placebo and ketorolac. Parecoxib doses of 5 mg or more were statistically superior to placebo. In **study 014** patients in moderate to severe pain were randomised to: placebo n=50; parecoxib 20 mg i.m n=51; parecoxib 20 mg i.v. n=50; valdecoxib 20 mg orally n= 50; ibuprofen 400 mg orally n=49; ketorolac 30 mg i.v. n=50; tramadol 100 mg orally n=50. Results were similar to those obtained in studies 003 and 004.

Study 025 in which patients (50/51 per group) received a single dose of parecoxib 20 mg i.m., parecoxib 20 mg i.v.; parecoxib 40 mg i.m., parecoxib 40 mg i.v, ketorolac 60 mg i.m., or placebo had an outcome for PID similar to the other dental pain studies. Time to use of rescue medication was approximately one hour in the placebo patients and over seven hours in the shortest of the active treatments.

Study 022 evaluated the efficacy of parecoxib administered prophylactically to dental patients 30 to 45 minutes prior to surgery. The median time to rescue medication was greater than 24 hours with a single 40 mg dose. However, the study did not compare preoperative with postoperative treatment.

- **Orthopaedic surgery**

Three studies were conducted in orthopaedic surgery, two of post-operative, and one of pre-operative treatment.

Study 018 was a single dose trial in patients undergoing elective knee replacement. Patients were randomized to: placebo n=37; morphine 4 mg n= 39; ketorolac 30 mg n 41; parecoxib 20 mg n = 43; parecoxib 40 mg n = 36 (all by i.v. administration). A single dose of parecoxib 40 mg IV provided analgesic efficacy significantly superior to that of placebo and the median time to rescue medication was markedly longer (310 min vs. 128 min). There were no statistically significant differences in the onset and extent of analgesic activity between parecoxib 40 mg IV and ketorolac 30 mg IV, while parecoxib 40 mg IV was superior to morphine 4 mg IV in these respects.

Study 020 was a single and multiple dose trial conducted in patients undergoing elective hip replacement. Patients were randomized to: placebo n=39; morphine 4 mg n= 38; ketorolac 15 mg n = 40; parecoxib 20 mg n = 43; parecoxib 40 mg n = 44. The study consisted of a one-day followed by a five-day phase. Results for pain intensity difference (one-day phase) were similar to those obtained in Study 018. Interpretation of the multiple day phase is difficult as only forty-three percent of patients entered it, however, the outcome appears to show that patients' global rating of analgesia was equivalent for the two doses of parecoxib and for ketorolac, but the conclusion can not be robust, given the numbers involved.

Study 037 was a trial in patients undergoing elective orthopedic surgery (knee/hip replacement or foot surgery). Test medications were given pre-operatively in order to prevent pain. As with study 022, this study did not compare preoperative with postoperative drug administration. Patients received a single, i.v. dose of parecoxib 20 mg, parecoxib 40 mg, or placebo 30 to 45 minutes prior to surgery. Efficacy was measured by Time to Rescue Medication and proportion receiving rescue medication. Rather surprisingly the outcome did not favour the active treatments, with the exception of the proportion taking rescue medication in the 20 mg parecoxib arm. However, in a (post-hoc) subset analysis, a significant difference with parecoxib sodium 40 mg when compared to placebo in the time

to rescue medication (10 hrs. 43 min. vs. 4 hrs. 18 min) in those patients that underwent bunionectomy was observed.

- **Gynaecological surgery**

Two studies where parecoxib was administered post-operatively to patients who had undergone total abdominal hysterectomy or myomectomy were conducted.

Study 019 Patients were randomized to a single intravenous dose of: placebo n=42; parecoxib 20 mg n= 39; parecoxib 40 mg n= 38; ketorolac 30 mg n=41; morphine sulfate 4 mg n=42. Results for PID and other criteria indicated equivalence of efficacy for the three non-steroidal anti-inflammatory drugs and superiority over placebo and morphine.

Study 021 consisted of a single-dose (up to 24 hours) and multiple-dose (up to five days) phase in patients who had undergone an elective abdominal hysterectomy or myomectomy. Treatments were: placebo n=45; morphine sulphate 4 mg n=38; ketorolac 30 mg n=42; parecoxib 20 mg n=38; parecoxib 40 mg n=41. The efficacy results of the single dose phase were similar to those of Study 019 and indicated equivalence of the non-steroidal treatments and superiority over placebo at most time points. Eighty-six (41%) patients were evaluable in the multiple-dose phase, of these only sixteen remained in the study by day three. Results for patients' global impression of analgesia on Day 2 were not statistically different between treatments.

- **Opiate-sparing**

Four studies examined the opiate sparing effect of treatment with parecoxib patients undergoing elective lower abdominal gynecological surgery, knee or hip replacement surgery or coronary artery bypass graft surgery.

Study 029 was in patients undergoing elective lower abdominal gynecological surgery. They were randomised to: parecoxib 20 mg n=73; parecoxib 40 mg n=70; placebo n=73. The primary efficacy measure was the amount of morphine consumed within 24 hours after the first dose of study medication, using patient controlled analgesia. Treatment differences were not statistically different; none of the four secondary efficacy variables showed significant differences.

Study 035 was in patients undergoing elective coronary artery bypass grafting (CABG). They were randomized 2:1 to parecoxib/valdecoxib 40 mg twice daily, or placebo. All patients had access to morphine sulfate through patient controlled analgesia. After a minimum of 72 hours, i.v. (parecoxib) was switched to oral (valdecoxib) treatment. Differences in total morphine consumption were statistically significant for the first 72 hours. However, there was a by-country interaction and if Germany and the United Kingdom where consumption was lower are removed the significance is lost.

Study 028 in hip replacement and **study 033** in knee replacement were submitted during the course of the centralised procedure. Both were conducted to a similar design. Adult patients undergoing surgery were randomised to placebo; parecoxib 20 mg i.v.; parecoxib 40 mg i.v. Treatments were administered with the first dose of morphine titrated in small boluses to patient comfort. Patients then self-administered morphine by patient controlled analgesia (PCA). Re-medication with parecoxib or placebo was at 12 and 24 hours after the first dose. The primary efficacy variable was the amount of morphine consumed within 24 hours of the first dose of study medication.

For Study 028 the differences in favour of active treatment were statistically significant ($p \sim 0.002$). For Study 033 the difference between placebo and parecoxib 20 mg is not statistically significant ($p = 0.105$); that between placebo and parecoxib 40 mg is significant ($p < 0.001$). These two new studies in hip and knee surgery show a morphine sparing effect allowing, very approximately, a 20 – 40% reduction in the dose of morphine.

It may be concluded that parecoxib and morphine can safely be used together and can result in a reduction in morphine dose through concomitant administration. However, the reduction did not appear to translate into a reduction in the side effects usually associated with morphine use, such as vomiting, nausea, constipation or respiratory depression. Whether its combined use translated into symptomatic benefit for the patient was an issue of concern. Together the CPMP did not consider that there was convincing benefit to the patient in terms of a reduction of the frequency or severity of opiate-related adverse events.

Clinical studies in special populations
No clinical trials have been conducted in children.

Clinical safety

A total of 3550 healthy subjects received either parecoxib sodium or valdecoxib via the intravenous, intramuscular or oral routes of administration; 1269 received placebo and 1205 received NSAIDs or other active comparators. Of the 2403 patients or subjects who received parecoxib sodium, 489 received the drug as IM injections. Most of the patients who received parecoxib sodium IM (n=453) were given a single injection. As the apparent safety profile of parecoxib is likely to change with the severity of the condition being treated, the data are considered under headings of the types of surgery involved.

- **Dental surgery**

There were no deaths or withdrawals from studies due to adverse events in the dental surgery programme. Adverse events do not lead to any impression of a dose response relationship with parecoxib. Indeed the frequency of events for low dose parecoxib was often higher than for high dose parecoxib.

A review of the data from six dental surgery trials show that the incidence of alveolar osteitis was numerically more frequent after parecoxib than after placebo, but considerable variability in the incidence rate was observed between the studies. A possible explanation for the great variability even between the placebo groups is that the investigators have used different criteria for the diagnosis of alveolar osteitis.

- **Orthopaedic and Gynaecological Surgery**

Just over six hundred patients have been treated with parecoxib at doses of 20 mg or 40 mg per day, in studies in orthopaedic and gynaecological surgery. Of these about sixty-five percent have received single dose treatments.

Deaths

There was one death; an 89-year-old man who was in the parecoxib sodium 20 mg treatment group died from a stroke nine days after study medication.

Study Withdrawals and frequent adverse events (see tables 3 and 4 respectively)

Table 3 AEs causing withdrawal of at least 1% of patients from the study

Event	**Placebo (n=305)**	**Parecoxib 20 mg (n=307)**	**Parecoxib 40 mg (n=302)**	**Morphine (n=162)**	**NSAIDS (n=165)**
Studies 018, 019, 020 and 037 (orthopaedic) and 021 and 029 (hysterectomy/myomectomy)					
Any event	3.6	3.6	4.6	3.7	6.1
Fever	0.3	0.3	0.0	0	3.6
Headache	0.7	2.0	1.0	1.9	2.4
Nausea	1.0	0.7	0.3	0.0	0.0

Table 4 Adverse events with an incidence of at least 3% in any treatment group

Event	Placebo (n=305)	Parecoxib 20 mg (n=307)	Parecoxib 40 mg (n=302)	Morphine (n=162)	NSAIDS (n=165)
Any Event	70.2	74.3	72.2	77.8	73.9
Abdominal fullness	5.2	3.6	2.0	3.7	3.0
Abdominal pain	6.6	6.2	6.6	8.6	9.1
Anaemia	3.9	3.6	4.6	3.7	2.4
Anxiety	2.0	2.0	2.3	4.3	1.2
Back pain	2.3	2.9	2.3	3.7	1.2
Confusion	2.3	1.3	1.0	3.1	1.2
Constipation	5.2	5.9	5.0	8.6	6.1
Dizziness	6.2	9.4	7.6	7.4	8.5
Dyspepsia	3	2.3	3.3	3.1	2.4
Excess sweating	1.0	2.6	1.3	1.2	3.6
Fever	17.7	8.8	7.6	16.3	23
Headache	9.5	9.1	8.6	7.4	15.2
Hypotension	1.3	2.3	3.3	1.9	4.2
Insomnia	2.3	3.6	0.0	4.9	4.8
Nausea	39	31.9	30.5	25.3	23.6
Pruritus	11.8	14.7	11.6	6.8	4.8
Reduced bowel sounds	1.3	1.6	0.3	3.1	1.6
Somnolence	5.2	3.3	2.3	8.6	7.9
Tachycardia	2.0	2.9	2.3	3.7	6.1
Vomiting	13.8	13.7	11.3	13.6	15.2

- **Coronary artery bypass surgery (CABG)**

Deaths

Four of the 311 patients (1.3%) randomised to parecoxib 40 mg b.i.d. died. None of the 151 patients on placebo died. Although none of the deaths was attributed to test treatment by the applicant or study events committee one patient developed renal failure and one gastrointestinal bleeding as the initial event in a sequence ultimately resulting in death.

Serious Adverse Events

Table 5 shows serious adverse events experienced in CABG surgery it should be pointed out that it is for the entire duration of the study (fourteen days).

Table 5 Serious adverse events in CABG patients – by treatment (%)

Event	Placebo	Active
Any Event	4.8	19.0
Abnormal renal function	0.0	1.9
Cardiac failure	1.9	1.2
Cerebrovasular disorder	1.3	4.8
DVT	0.0	1.0
Elevated creatinine	0.0	1.3
GI bleeding	0.0	1.3
Myocardial infarction	0.6	2.9
Pleural effusion	1.3	2.6
Pneumonia	4.0	1.6
Wound dehiscence	0.0	1.6
Wound infection	0.0	1.6

In the cardiac surgery study, there was a trend of a higher incidence rate of cerebrovascular events in patients receiving parecoxib/valdecoxib compared to placebo. Such events seem to be associated to known risk factors (cerebrovascular disease, hypertension, advanced age, aortic atherosclerosis, atrial fibrillation, diabetes). An appropriate warning has been included in the SPC.

Safety in Pre-operative administration studies

The type, frequency and severity of adverse events observed in the pre-operative administration surgery studies were similar to those observed in comparable surgical models in which parecoxib was administered post-operatively

Safety in special populations

- Renal impairment

Experience with parecoxib in patients with renal dysfunction is limited to one study. In the renal impairment study patients with normal, mild, moderate, and severe impairment, and those on haemodialysis received single doses of 20 mg parecoxib i.v. and oral valdecoxib. The effects of renal impairment on drug related substance were studied, as were the effects of the drug on renal function. The results for valdecoxib following i.v. parecoxib do not indicate any serious safety problem should the drug be unknowingly given to patients with renal impairment. Also there seems to be little, if any, effect of single administration of the product on renal function as judged by renal clearance studies before and after exposure (Table 6). However it is recommended that parecoxib is used with caution in patients with renal impairment.

Table 6 The effect of valdecoxib following i.v. parecoxib in renally impaired patients

	Normal (n=20)	**Mild (**n=10)	**Moderate** (n=8)	**Severe** (n=11)	**Dialysis** (n=12)
Renal clearance mL/min/1.73m^2 (mean & range)	91 (81-115)	64 (50-77)	37 (31-46)	17 (7-28)	----
AUC $_{0 \rightarrow \infty}$ (ng.hr/mL)	2768	3756	2989	3562	3133
Cmax (ng/mL)	385	385	302	288	265
T1/2	8.67	11.8	10.7	14.1	9.93
Renal CL (L/hr)	0.18	0.12	0.09	0.04	---
Nonrenal CL (L/hr)	6.44	4.76	5.98	5.79	---

- Elderly

One hundred and fifty seven patients over the age of seventy-five have been included in the database from two new surgical studies. Comparison of the safety profile in those patients with that in patients younger than seventy-five does not lead to any evident differences. Despite the lack of rigour of the negative finding of no difference, the data base contains over 150 patients more than seventy-five years old which seems a reasonable number albeit not 'powerful' enough to find a difference between the elderly and non-elderly.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

In general the quality of this product is considered to be acceptable and indicates that the active substance and finished product are manufactured and controlled satisfactorily and in compliance with current EU guidelines. Satisfactory information has been provided to show that these manufacture and control processes are well controlled, routinely and consistently generate a product of uniform quality and should perform in a reproducible way in practice when used in accordance with the instructions defined in the SPC.

Preclinical pharmacology and toxicology

The preclinical studies have adequately characterised the pharmacology and toxicology of the compound. Carcinogenicity studies were not conducted, but since parecoxib is intended for short-term use only this was considered to be acceptable. This information has been included in the SPC.

Efficacy

Parecoxib is effective in relieving moderate to severe post-operative pain. As there is limited clinical experience beyond 2 days, parecoxib is recommended for short term use. The opiate-sparing effect of parecoxib has been described in section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SPC.

Safety

Evaluation of the safety of parecoxib is complicated by the surgical background. The nature of the procedures varied from very low risk, through intermediate risk, to high risk, (coronary artery bypass grafting CABG). Many of the adverse events are attributable to surgery rather than the investigational drug treatments and their nature and frequency will obviously vary with the type of surgery. The study in CABG is different to the others in that it was of longer duration, the patient population was of higher risk, and the safety profile of parecoxib seemed less favourable that in other studies. Therefore the SPC has been amended to indicate that CABG patients may have a higher risk of serious adverse events, also identifying those serious adverse events.

Benefit/risk assessment

Based on the CPMP review of the data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Dynastat (parecoxib sodium) was favourable for the '*short term treatment of postoperative pain'*.

6. Post marketing experience

The CPMP has been made aware of reports of serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with valdecoxib, the active metabolite of Parecoxib sodium. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides. It is possible that such reactions may also occur with the use of Parecoxib sodium.

As of September 26, 2002, a total of seven case reports with fifteen adverse events associated with the use of Parecoxib sodium have been received by the MAH. The reports include allergic reaction, breathlessness, increased heart rate, vertigo and injection site abscess. The estimated exposure since launch is approximately 140,000 patients. So far, there have been no reports of serious skin reactions and only one report of serious hypersensitivity reaction associated with parecoxib sodium administration.

However, in order to prevent the occurrence of such serious reactions, the Product Information of parecoxib sodium has been revised through an Urgent Safety Restriction procedure during October 2002 CPMP to inform prescribers that parecoxib is contraindicated in patients with a history of hypersensitivity to sulphonamides. Moreover, it informs that in post marketing experience, hypersensitivity reactions including anaphylaxis, angioedema and serious skin reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with valdecoxib and may also occur with parecoxib. The patient leaflet has also been revised accordingly.

Safety issues assessed through an Article 31 referral procedure started in July 2002.

Further to a request from France, the CPMP, during its meeting held from 23 to 25 July 2002 decided to start a referral procedure under Article 31 of Directive 2001/83/EC as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib. The questions identified related to gastrointestinal and cardiovascular safety. In October 2002, the CPMP asked additional questions relating to serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with COX-2 inhibitors.

The conclusions for medicinal products containing parecoxib are as follows:

- Gastrointestinal toxicity

Available data indicate that significant and consistent gastrointestinal benefit of COX-2 inhibitors compared with conventional NSAIDs has not been demonstrated. Parecoxib showed a better tolerability than NSAIDs with regard to gastrointestinal effects. However these conclusions are based on very limited data from clinical studies and little usage experience in the post-licensing period, and are insofar preliminary. Furthermore, no data on safety in post surgical patients with regard to stress ulcer are available.

Therefore, a general statement has been added in section 4.4 "Special warnings and special precautions for use" and 5.1 "Pharmacodynamic properties" of the SPC for all COX-2 inhibitors relating to patients at risk of developing gastrointestinal complications with NSAIDs.

It is unknown whether the gastrointestinal toxicity profile of COX-2 inhibitors in association with acetylsalicylic acid is inferior to conventional NSAIDs given with acetylsalicylic acid but there is no evidence to suggest it would be superior. Based on the current data on parecoxib the product information should be updated to include the potential for increase in gastrointestinal toxicity compared with COX-2 inhibitors or acetylsalicylic acid alone.

Further to discussions and considering the assessment of the data presented for all the COX-2 inhibitors, the section 4.4 "Special warnings and special precautions for use" of the SPC has been updated regarding concomitant use of all COX-2 inhibitors with a general statement on COX-2 inhibitors and acetylsalicylic acid association.

- Cardiovascular toxicity

The available pre-clinical data raised concern about cardiovascular (CV) safety, in particular myocardial infarction (MI), however, conflicting clinical results have often been obtained. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. In comparison to placebo there may be an increased risk for thromboembolic events in high cardiovascular risk patients. However, the database is very limited. The database is also very limited for comparisons versus conventional NSAIDs. Therefore, parecoxib use is not recommended in high cardiovascular risk patients undergoing major surgeries.
With respect to CV risk, it can be considered that there may be a small safety disadvantage of COX-2 inhibitors compared to conventional NSAIDs. Therefore, the SPC has been updated for all COX-2 inhibitors, including parecoxib, in its section 4.4 "Special warnings and special precautions for use" by adding a warning statement for patients with a medical history of cardiovascular disease or those using low dose of ASA-treatment for prophylaxis of cardiovascular thrombo-embolic diseases.

- Hypersensitivity and serious skin reactions

The Product Information of parecoxib sodium was revised through an Urgent Safety Restriction procedure during October 2002 CPMP.The statement in section 4.4 "Special warnings and special precautions for use" relating to hypersensitivity and serious skin reactions with Dynastat was then already in line with the adopted conclusions resulting from this referral procedure. Therefore, no update was requested at this stage.

- Conclusion

Further to the finalisation of the referral procedure under Article 31 of Directive 2001/83/EC as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, gastrointestinal and cardiovascular data have been updated in the SPC and in the PL for Dynastat:

- to promote the safe use of Dynastat by adding or strengthening warnings, in particular recommending caution for patients with underlying gastrointestinal and cardiovascular risks,
- to include the potential for increase in gastrointestinal toxicity compared with COX-2 inhibitors or acetylsalicylic acid alone,
- to add a warning statement for patients with a medical history of cardiovascular disease or those using low dose of ASA-treatment for prophylaxis of cardiovascular thrombo-embolic diseases.