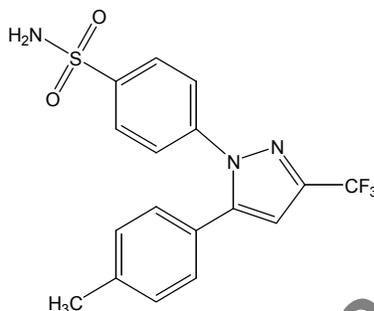


SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Onsenal. This scientific discussion has been updated until 1 May 2004. For information on changes after this date please refer to module 8B

Introduction

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulphonamides (e.g. thiazides, furosemide) but differing from arylamine sulphonamides (e.g. sulphamethoxazole and other sulphonamide antibiotics).



Celecoxib is a selective inhibitor of cyclooxygenase-2 (COX-2) with no inhibition of cyclooxygenase-1 (COX-1) at therapeutic doses. Cyclooxygenase is responsible for generation of prostaglandins. The COX-2 isoform is not detected in most normal tissues and is under the control of an inducible promoter, and its expression is associated with inflammation. Elevated levels of COX-2 are found in many pre-malignant lesions (such as adenomatous colorectal polyps) and epithelial cancers. COX-2 is probably 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).

Celecoxib has been approved within the EU via the mutual recognition procedure as a non-steroid antiinflammatory drug for symptomatic relief in osteoarthritis and rheumatoid arthritis.

Onsenal (celecoxib) is intended for the treatment of Familial Adenomatous Polyposis (FAP), a genetic disease with a prevalence of between 0.3 to 1 in 10,000 persons within the EU, resulting from an autosomal dominant genetic alteration of a tumor suppressor gene, the adenomatous polyposis coli (APC) gene. Polyps with the APC mutation overexpress COX-2 and affected patients usually develop multiple premalignant adenomas in the colon and rectum between 12 and 16 years of age. The average number of polyps in FAP patients is around 1,000, but this may vary between 100 and 2,500. Polyps are usually evenly distributed from caecum to rectum and up to 93% of the patients have involvement of the duodenum. Presenting symptoms appear usually at around 25-30 years of age and are characterised by rectal bleeding, diarrhoea or constipations and abdominal pain. These tumours are not life threatening *per se*, but if left untreated, polyps continue to form and enlarge in the colon or rectum resulting in essentially a 100% chance of developing colorectal cancer at around 40-50 years of age.

The current standard therapy in the EU is endoscopic surveillance and surgery. Treatment is polypectomy until the late teens when proctocolectomy with ileo pouch-anal anastomosis is performed. Adenomas and eventually also cancer may develop in other parts of the gastrointestinal tract, in particular the duodenum. Patients with extensive duodenal disease are subjected to pancreatoduodenectomy or Whipple's operation. The surgical approach is often highly mutilating, especially considering the relatively young age of affected patients, and it is proportional to the anatomic extension of the disease.

Several clinical and epidemiological studies have demonstrated that extended periods of NSAID intake is associated with a 40-50% reduction in the incidence of colorectal cancer and a decreased risk of developing adenomas. Small and methodologically less optimal studies have indicated that the NSAID sulindac may reduce the number and size of polyps in patients with FAP. Treatment is, however, limited by gastrointestinal side effects related mainly to the inhibition of COX-1.

Inhibition of COX-2 leads to inhibition of angiogenesis and tumour cell proliferation as well as the induction of apoptosis. Thus, COX-2 stimulation may be one important common step in the pathway leading to adenomas and colorectal cancer regardless of the underlying genetic defect and COX-2 inhibition may represent a significant therapeutic option in the prevention and/or regression of adenomatous polyps.

Onsenal (celecoxib) is indicated for *“the reduction of the number of adenomatous intestinal polyps in Familial Adenomatous Polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated.”* Treatment with celecoxib in FAP has been studied for up to 6 months and has not been shown to reduce the risk of gastrointestinal or other forms of cancer or the need for surgery. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and FAP-related surgery should not be delayed (see clinical discussion).

The proposed dosage regimen of Onsenal is two 200 mg capsules administered twice per day orally, taken with food. The maximum recommended daily dose is 800 mg.

2. Chemical, pharmaceutical and biological aspects

Composition

Onsenal contains 200 and 400 mg of celecoxib as active ingredient. It is presented in hard gelatine capsules. The two strengths only differ in terms of amount of granulate filled into the capsules.

Other ingredients include lactose monohydrate, sodium lauryl sulphate, povidone K-30, and croscarmellose sodium and magnesium stearate.

Onsenal 400 mg capsules are packaged in opaque PVC/foil blister strips, while Onsenal 200 mg capsules are packaged in clear or opaque PVC/Aclar/foil blister strips.

Active substance

Celecoxib is a diaryl substituted pyrazole. Its chemical name is (4-[5-(4-Methylphenyl)3(trifluoromethyl)-1 H-pyrazol-1 -yl]benzenesulfonamide. It does not contain any chiral centers and thus it does not exhibit any optical isomers.

Celecoxib is a member of the class of anti-inflammatory agents known as specific cyclooxygenase-2 (COX-2) inhibitors. It is a white to off white solid, composed of crystalline particles with a needle and bar habit. The amide hydrogen is weakly acidic (pK_a is near 11) leaving the molecule uncharged at physiological pHs. Celecoxib is hydrophobic ($\log P$ is 3.5) and is practically insoluble in aqueous buffers at a range of physiological pHs. It is however a highly permeable compound and it is categorised into Class II according to the US Biopharmaceutics Classification System (BCS). Therefore particle size effects on dissolution of capsules can be expected. In order to ensure batch to batch consistency celecoxib is subject to milling.

Three polymorphic forms of celecoxib, distinguishable by powder X-ray diffraction (PXRD) have been isolated. Solid-state interconversion between the forms at low temperatures has not been observed. All GLP lots of celecoxib consisted of stable Form III polymorph. Following pin milling only the thermodynamically stable polymorph, Form III, is produced.

Two processes, Process A and Process B, may be used for the preparation of celecoxib. The differences are mainly in the use of different reagents and solvents. Process B offers an improved

manufacturing efficiency by producing celecoxib that does not require further purification by recrystallisation. Celecoxib produced by either process is chemically and physically equivalent. Synthesis involves a two-step process from the starting materials 4-methylacetophenone and ethylflouroacetate, which are reacted to form an intermediate product and then celecoxib. The product is milled using a pin mill or equivalent apparatus to reduce the particle size. There are eleven potential impurities arising from the routes of synthesis. All these impurities are detected by the current analytical release methods for celecoxib. Seven impurities have been identified in one or more batches of celecoxib used in animal studies and/or clinical trials. A potential impurity is 4-SAPH, which is mutagenic and potential carcinogenic. However, data from 50 batches have been provided demonstrating that 4-SAPH was below the detection limit (<25 ppm) in all cases.

Specifications of the Active Substance

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), related impurities (HPLC), particle size (LLD), residual solvents (GC), heavy metals (Ph. Eur.) etc.

Particle size is measured and evaluated, as it is critical to the bioavailability, dissolution and content uniformity of the encapsulated product. Specifications have been selected that set both the upper and lower limit of the particle size distribution. The D90 limit is justified based on the results from a bioequivalence study of capsules containing different particle sizes. Process validation of the milling step is provided. It demonstrates that the milling process is a robust method and is well controlled by particle size analyses in bulk drug substance prior to release.

Batch analysis data have been provided for 53 batches of the active substance. Comparative batch analysis data from three full-scale batches manufactured at different sites are presented showing no significant differences. Furthermore, three full scale batches manufactured by process A and B respectively have been compared demonstrating no differences in terms of physicochemical characteristics and impurity profile.

The analytical methods used in routine controls were adequately validated and thus considered suitable. Impurity limits in the specification are justified by toxicology studies.

It has been proved that the tests and limits in the specification are appropriate for controlling the quality of Celecoxib.

Stability of the Active Substance

Stability evaluation has been performed in accordance with ICH guidelines. The parameters tested are assay, degradation products, water content and melting range using the same methods as for release. Results for three pilot batches and twelve production scale batches produced by Process A and for three production scale batches produced by Process B are presented. The results for Process A material cover up to 48 months at 25°C/60% R.H., 6 months at 30°C/60% R.H., and 6 months at 40°C/75% R.H. For Process B material, results are available for 9 months at 25°C/60% R.H., and 6 months at 40°C/75% R.H. No degradation products were observed at all storage conditions at all time points. There were also not observed any differences in the degradation or impurity profile of the two manufacturing processes.

A forced degradation study has demonstrated that celecoxib does not degrade under the acid, base and oxidising stressed conditions used. Furthermore results from a photostability study indicate that the active substance is stable under UV and visible light conditions.

Therefore the requested retest period when the product is packaged in double polyethylene bags in a fibre container and stored under the defined conditions can be approved.

OTHER INGREDIENTS

All excipients comply with Ph Eur. requirements. Sufficient information has been provided showing that lactose monohydrate, croscarmellose sodium, magnesium stearate and gelatin capsules do not present any risk for TSE. For magnesium stearate and gelatin CEP's are given. For lactose monohydrate it is declared, that milk from healthy animals in the same condition as milk collected for

human consumption is used. Therefore there are no concerns relating to TSE risks arising from the excipients.

Two different pack types are proposed as immediate packaging material. Clear or opaque PVC/Aclar/foil blister strips and opaque PVC/foil blister. The materials are tightly controlled by in house specifications. The compatibility of celecoxib capsules with the container/ closure is demonstrated by stability data.

Product development and finished product

Celecoxib is practically insoluble in water and is isolated as agglomerates of needle-shaped crystals, which exhibit cohesive behaviour and poor flow properties. The aim of the initial formulation studies was to develop a homogeneous powder with good flow characteristics and producing a bioavailable dosage form.

Celecoxib is classified as a low solubility/high permeability drug. Particle size control has been found to be critical to the content uniformity, dissolution and bioavailability of the product. For this reason special attention is given to particle size, and an adequate specification is set, based on the results from the bioequivalence study.

Two different dissolution methods have been developed. The drug substance is poorly soluble in water and therefore it was necessary to use a dissolution method with non-physiological pH of 12, and 1 % SLS added to obtain sink conditions. Due to the very low solubility of Celecoxib in physiologically relevant medium no clinically meaningful in vivo-in vitro correlation has been possible to establish. Nevertheless there have been no concerns over the availability of the substance as presented in the summary of clinical pharmacokinetics.

Because of cross-linking of the gelatine capsules when stored at accelerated conditions, it was necessary to develop an alternate test (Tier II) with enzyme pre-treatment. When using this test, no difference in dissolution is observed compared to initial results with the normal test. There is no evidence that the bioequivalence of capsules is adversely affected by cross-linking or pellicle formation. This dissolution test is used primarily as a batch quality control measure to ensure that capsule shells dissolve and their contents go into solution and there is no relevance of the dissolution method to the in vivo behaviour.

Several formulations of the finished product have been developed. The formulations used for phase III clinical trials are identical to the formulations which are intended to be marketed.

The method of manufacture is a typical wet granulation and fluid bed drying method, followed by milling and capsule filling. In process controls are stated. Validation data from three full-scale batches of both the 200 and 400 mg capsules are provided. Granulation and milling were fully validated with respect to content uniformity, reproducibility, particle size, bulk density. Weight control data were within acceptance criteria. Assay, dose uniformity and dissolution results confirm that the process is capable of consistently producing a uniform drug product with the required unit dose strength and dissolution performance. All batches met the acceptance criteria for the release of the final product and all pre-defined quality and performance specifications established in the approved validation protocol was met.

Product specification

The products specifications include tests by validated methods for appearance, identification (HPLC, UV), assay (HPLC) degradation products (HPLC), uniformity of mass (Ph.Eur.), dissolution and microbial purity. Batch analysis data from 21 lots for 200 mg capsules and 3 lots for 400 mg capsules are presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release. Results from two lots (200 mg) manufactured using drug substance made via Process B compare favourably with a commercial lot manufactured using drug substance made via Process A.

The specification of the finished product complies with the requirements set in the current guidelines. Batch analyses data, supporting the limits applied for, are submitted for full-scale batches as well as development batches.

Stability of the product

All stability studies were conducted in compliance with ICH requirements. The batches are tested for all parameters included in the release specifications with the addition of disintegration and water content.

For the 200 mg strength primary stability studies have been performed for 36 months stored at 25°C/60% RH, 24 months 30°C/60% RH and 6 months 40°C/75% RH. For the 400 mg strength data have been provided for three lots stored for 13 months at 25°C/60% RH and 30°C/60% RH and for 6 months at 40°C/75% RH. During these studies all parameters remain within the defined specifications despite of the storage conditions used.

Photostability of the drug product has been evaluated and results from assay, degradation, dissolution and appearance testing indicate that 200 mg and 400 mg capsules are not sensitive to light.

Forced degradation studies were conducted on the Phase III formulation celecoxib capsules. Results showed that substantial degradation occurs only under extreme thermal conditions (130°C) and that the HPLC analytical method is stability indicating.

As suggested by the results obtained from all batches, the proposed shelf life for the commercially packaged product under the conditions specified in the SPC is acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Onsenal is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. Two additional dissolution tests had to be developed in order to allow sink conditions of the poorly soluble active substance and to overcome the cross linking phenomenon that might be present at capsules stored at accelerated conditions resulting in reduced in vitro dissolution values. Nevertheless, there have been no concerns over the availability of the substance as presented in the summary of clinical pharmacokinetics.

The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process of the finished product has been adequately described.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

However at the time of the CPMP opinion a number of minor quality issues were unresolved. The applicant gave a commitment to resolve these issues as a post opinion follow up measure:

- Acceptance criteria and tests methods for all the excipients should be harmonised with Ph.Eur.

3. Toxicopharmacological aspects

GLP

All toxicology studies were conducted in accordance with Good Laboratory Practices (GLP), and relevant EU and ICH guidelines. However, the dose-ranging and exploratory studies and “core” safety pharmacology studies were not conducted in compliance with GLP but did conform to current good scientific practices. Overall, compliance with GLP is satisfactory.

Pharmacodynamics

In vitro studies

Celecoxib was shown to exhibit preferential COX-2 inhibition as compared to COX-1. It is noted, however, that the *in vitro* determinations were dependent upon experimental conditions, and do not adequately address the relationship between pharmacokinetic/ pharmacodynamic parameters that might influence COX-2-selectivity *in vivo*. Experiments with the carrageenan-inflamed air pouch rat indicated that celecoxib caused inhibition of COX-2 comparable to a variety of conventional NSAIDs but at slightly higher dosages (x 2-3). The mechanism of COX-2 selectivity was shown to be due to time-dependent inhibition of COX-2 and reversible competitive inhibition of COX-1. By the use of crystallographic methods it was shown that the phenylsulfonamide moiety of celecoxib bound in a side pocket present in the active site of COX-2 but not COX-1.

In vivo studies

The two most relevant pre-clinical models for the human Familial Adenomatous Polyposis (FAP) are the (Apc) Multiple Intestinal Neoplasia (Min) mice model and the AOM rat model.

The Min mice inherit a dominant mutation in the Apc gene. Homozygosity for the Min mutation is embryonically lethal. Heterozygous Apc +/Apc (Min) Min mice develop more than 100 intestinal tumours per mouse, mainly located in the upper gastrointestinal tract. The adenomas grow to a detectable size in one to three months and visible tumours begin to arise in the Min mice around 55 days of age. The Min mice usually get moribund from tumour burden at age 80 days and seldom live longer than 140 days due to intestinal bleeding and the resulting severe anaemia.

In this model celecoxib showed a dose-dependent decrease in tumour indices with the most striking change occurring in the middle and distal small intestines when administered between days 30 to 80.

Total tumour multiplicity decreased in a dose-dependent manner to 29% of the control group ($p < 0.001$) in mice treated with 1500 ppm (days 30 to 80). However, no obvious effects occurred at the lower dose levels.

Further, celecoxib was evaluated in F344 rats given azoxymethane (AOM). AOM produces chemically induced colon cancer in the rat, the experimental endpoints being tumours (number or volume) and/or aberrant crypt foci (ACF) (putative preneoplastic lesions) depending on study design.

In a 50 weeks study, dietary administration of celecoxib (1500 ppm) was shown to inhibit both the incidence and multiplicity of colon tumours by 93% to 97%, respectively. Celecoxib was also shown to suppress the overall tumour burden by more than 87%. However, the variability was high.

(N=15)	% rats with gross tumours	Total No. of gross tumours /rat (mean \pm SD)	Tumour volume (mm ³) (mean \pm SD)
AOM	85%	1.91 \pm 1.38	204 \pm 483
AOM + celecoxib 1500 ppm	6%	0.06 \pm 0.23	27 \pm 23

In another study celecoxib, administered by diet for 16 weeks, was shown to reduce the numbers of AOM-induced ACF at 1500 ppm (3.5 μ g/ml) from 31% up to 42%, which was on a similar level as was shown in the treatment group receiving sulindac.

N=12 (males)	Total No. of ACF/rat	% change from controls (AOM + placebo)	Number of multicrypt per focus (4+)	% change from controls (AOM + placebo)
AOM	120 \pm 15	-	35 \pm 8	-
AOM + placebo	111 \pm 35	100%	31 \pm 10	100%
AOM + celecoxib 150 ppm (0.5 μ g/ml)	127 \pm 13	+14%	33 \pm 7	+6%
AOM + celecoxib 1500 ppm (3.5 μ g/ml)	71 \pm 15	-36%	18 \pm 6	-42%
AOM + Sulindac 320 ppm	77 \pm 14	-31%	21 \pm 6	-32%

In a 52-week study celecoxib administered by diet (500 ppm, 1000 ppm or 1500 ppm) to F344 rats has shown a significant dose-dependent reduction of both incidence and multiplicity of colon cancers.

Tumor volumes were also reduced in a dose dependent manner. The effect exerted by celecoxib at 1500 ppm was more marked in the early stage than in the late stage of carcinogenesis induced by AOM (77% vs 47% incidence; 84% vs 57% multiplicity). The steady state plasma levels of celecoxib in this study were 2.21, 2.61, and 4.29 µg/ml in the 500, 1000, 1500 ppm groups, respectively.

Pharmacodynamic drug interactions

No pre-clinical interaction studies were submitted.

General pharmacodynamics and safety pharmacology

Celecoxib has been studied in various animal models of inflammation and pain. COX-1 and COX-2 inhibitory action was studied and celecoxib was screened for a broad range of receptors and enzymes. The effects were related to COX-2 inhibition. There was an inhibition of platelet aggregation induced by arachidonic acid at concentrations of 0.3 to 10 µg/ml.

Relevant organ systems were investigated and there were no major findings in the safety pharmacology programme conducted.

Experimental evidence indicates that COX-2 has functional effects in the gastrointestinal tract. In rodents with preexisting gastrointestinal injuries, selective inhibition of COX-2 reduced mucosal prostaglandin synthesis and significantly enhanced the severity of colonic damage (colitis model) or inhibited ulcer healing (ulcer model). Other studies suggest that COX-2 plays a critical role in the resistance to gastrointestinal tract injury following exposure to a mild irritant, and that blockage of COX-2 inhibits the defence mechanism. As a consequence, the COX-2 'selective' profile of celecoxib may raise a potential safety concern with regards to ulcer healing (retardation) when episodes of blood per rectum and intestinal anastomotic ulceration occurs as observed in the one pivotal clinical trial with celecoxib. The role of celecoxib's COX-1 inhibitory action at high exposure levels in the bleeding episodes observed in the clinical trials is uncertain.

Pharmacokinetics

Plasma concentrations were analysed by HPLC, LC-MS assays. ¹⁴C-labelled celecoxib was used for studies of absorption, tissue distribution, metabolism and excretion.

Absorption differed between the rat (approximately 60%) and the dog (approximately 17%). Binding to plasma proteins was studied both *in vitro* and *in vivo* over a range of concentrations, and ranged from 94% to 98% in mouse, rat, dog and man. The rabbit, however, had lower protein binding, and it is estimated that the 'free drug' exposure in this species is two-fold that of man.

The volume of distribution indicates that celecoxib is readily distributed into tissues (V_d 2-3 l/kg in the species studied). Celecoxib was distributed to primarily the gastrointestinal tract but high concentrations were also observed in the liver, red blood cells, adrenal and lachrymal glands and bone marrow. Celecoxib has been shown to pass the blood-brain barrier, to pass the placenta and to be excreted in milk.

No accumulation phenomenon was observed. Celecoxib is hydroxylated and further oxidised to carboxylic acid and cleared by hepatic cytochrome P450 enzymes. Dimorphism was observed in rat and dog (CYP2D15, CYP2C21) but the celecoxib metabolites were present in the animal species used for safety assessment. Human dimorphism also exists due to allelic variants of CYP2C9 (warfarin and tolbutamide metabolic interaction). However, the main celecoxib metabolites are inactive towards COX isoforms. Gender differences in clearance were observed in the rat and mouse. Celecoxib is the major circulating substance in rats, dogs and humans. Excretion in animals (except female mice) is predominantly by the biliary route. In man, the metabolites are mainly excreted with urine.

Toxicology

Single dose toxicity

Single dose toxicity studies with oral administration of celecoxib were conducted in rats, dogs and Cynomolgus monkeys. No important high-dose acute toxicity was observed following administration of 2000 mg/kg of celecoxib in rats and dogs and it was concluded that the approximate lethal dose was greater than 2000 mg/kg body weight. Furthermore, celecoxib did not show to be a potential sensibiliser or an irritant product.

Celecoxib was not acutely lethal in female cynomolgus monkeys after oral administration of doses ranging from 2 to 15 times the maximum recommended human dose (MRHD) that is proposed for treatment of FAP (400 mg BID, approximately 16 mg/kg/day based on a body weight of 50 kg). Due to the observation of very low absorption in the Cynomolgus monkey the study programme in monkeys was discontinued.

Repeat-dose toxicity

Repeat-dose toxicity was investigated in Sprague-Dawley rats (up to 26 weeks) and Beagle dogs (up to 52 weeks of administration).

In rats, gastrointestinal toxicity and associated events were dose limiting. Female rats were more affected than males because of a gender-specific 4-fold lower clearance and a resulting double systemic celecoxib exposure. NOEL was established at 20 mg/kg/day providing a mean C_{max} of 2 to 4 µg/ml and an AUC_{0-24h} of 19 to 53 µg/ml *h (gender and duration dependent).

In the studies undertaken in the dog, celecoxib was administered twice daily taking into account its short half-life and proposed clinical dose regime. Histopathological examination was performed in the control and high-dose groups in the pivotal dog studies and no overt toxicity was observed at the highest dose level. There was a wide variation in systemic exposures in dogs given the same dose levels of celecoxib due to the two cytochrom P450-dimorphic populations of dogs (PM and EM). The NOEL in dogs was the high dose level of 17.5 mg/kg BID, which corresponds to a C_{max} of 1.5 to 3.6 µg/ml and an AUC_{0-24h} of 11 to 41 µg/ml *h (gender and duration dependent).

The NOAELs in rats corresponded to an exposure 4-5 times (in respect to C_{max} and AUC respectively) higher than the clinical exposure in humans in a 4-week study, while in the 13- and 26-week studies and all studies in the dog, the exposures was almost the same as in the clinical setting or very slightly higher.

In particular in dogs, if fast clearance animals are considered, the safety factor for GI toxicity appears lower than the unit (0.99 and 0.6 for C_{max} and AUC respectively). Also considering rats in the 4-week study the safety factors appear 50% reduced. Thus in studies where the NOAEL approached the MRHD proposed for the FAP indication (i.e. 800 mg/day corresponding to about 16 mg/kg), the ratio between animal exposure /human exposure was not really significant as demonstrated for the 400 mg/day dose previously approved for rheumatoid arthritis, on the basis of the same preclinical toxicity studies.

In the pharmacodynamic colon cancer models only C_{max} was measured. Thus, it is not possible to make a complete comparison between exposure levels at therapeutic doses in the colon cancer models and NOAEL or lowest toxicity dose in the same animal species (in order to exclude interference of species-related toxicokinetics), and finally with the MRHD. From the evaluation of C_{max} it appears that there is a non-significant safety margin in the same animal species between non-toxic doses and therapeutic ones, and also with MRHD. In mice a safety margin of 3.4-1.3 with respect to MRHD was observed.

Genotoxicity

Celecoxib was tested in an appropriate battery of genotoxicity assays including gene mutation in bacteria and mammalian cells (CHO), chromosomal aberrations *in vitro* (CHO) and *in vivo* (rat micronuclei in bone marrow). Endo-re-duplication was observed in CHO cells *in vitro* after metabolic

activation but the relevance of this finding is not known and is unlikely to indicate a clastogenic potential. No bone marrow toxicity or signs of toxicity were observed in the *in vivo* rat assay with a three-day treatment protocol. However, information of exposures from other studies indicates that saturation of exposure occurs at the high dose selected in the *in vivo* genotoxicity test. It may be concluded that celecoxib is unlikely to be genotoxic under the proposed clinical conditions.

Carcinogenicity

The carcinogenic potential and chronic toxicity of celecoxib was also investigated in 2-year bioassays in CD-1 mice and SD rats. Gastrointestinal toxicity and associated secondary dose-limiting effects were observed in both animal species. Trends for higher incidence of hemangiosarcomas (male mice), pituitary pars distalis adenomas (female mice) and hepatocellular adenomas/carcinomas (male rats) were observed. However, the incidences of these appeared to be within the values of historical controls.

MTD was reached in both experiments at exposure levels close to or lower than that expected in the proposed clinical use in FAP patients. In mice the AUC_{0-24h} was 6 to 27 µg/ml*h across all groups given celecoxib (exposures were slightly higher in male compared to female mice). In rats high dose exposures were in the range of 57 to 158 µg/ml*h (AUC_{0-24h}, the higher range in female rats), around the range of expected human exposure in FAP patients.

Although the experimental exposures *in vivo* were low as compared to those in the proposed clinical situation, the overall conclusion is that the carcinogenic potential of celecoxib is low. The tumour findings in the 2-year carcinogenicity studies should not compromise the proposed use of celecoxib in man (at double dose level as compared to the OA and RA indications).

Reproductive and developmental toxicity

A standard reproduction toxicity testing battery was conducted (segment I, II, III in rats, and segment II in rabbits). Male fertility including testicular function was not affected by celecoxib. As expected, celecoxib-induced inhibition of prostaglandin synthesis caused early embryo-foetal deaths in the rat. Further, celecoxib given during organogenesis selectively caused diaphragmatic hernia in rat offspring. In rabbits, celecoxib caused selectively embryo-toxicity, embryo-lethality, and malformations of heart and major vessels including defects of aorta, the pulmonary artery and ventricular septal defects. The effects of celecoxib on the parturition processes have not been evaluated. Celecoxib has been shown to cross the placenta and is secreted into milk. Toxicity was observed in the F₁ generation offspring after administration of celecoxib to their pregnant and lactating mothers possible due to offspring exposure via *in utero* exposure and/or milk. Systemic exposure levels at respective NOELs were close to or lower than those expected exposures in FAP patients proposed to be given 400-mg celecoxib on a chronic basis.

Celecoxib affects fertility due to the increased pre- and post-implantation losses seen in rat and rabbit, reduced gestation index and increased length of pregnancy in rat. The results of rat and rabbit teratology studies suggest that Celecoxib acts as a teratogen in both species without any treatment-related clinical sign or change in body weight of dams. The induced diaphragmatic hernia is the same phenotype as occurred spontaneously in maternal animal, suggesting the presence of a genetic susceptibility background.

Celecoxib was shown to selectively induce malformations and embryo-lethality in early pregnancy.

Local tolerance and immunotoxic potential

Dermal sensitisation potential of celecoxib was negative according to the Magnusson and Kligman guinea pig model. Celecoxib did not produce a reaction indicative of active systemic anaphylaxis or homologue/heterologous passive skin anaphylaxis in animal stimulation assays. The antigenic potential of celecoxib may be regarded as low, except for possible sulphonamide sensitivity.

Celecoxib was non-/minimal irritant to skin and eye. Celecoxib does not contain a chiral centre, and thus no stereoisomers exist. Celecoxib will not be expected to carry a risk for dependence or addiction.

Environmental risk assessment

No particular risks to the environment of celecoxib use in FAP patients can be foreseen.

Discussion on toxico-pharmacological aspects

Celecoxib selectively inhibits COX-2, but also COX-1 although not at therapeutic dose levels. The pharmacodynamic rationale for celecoxib in FAP is its COX-2 inhibitor effect, possibly its molecular configuration independently of its COX-2 inhibition, or perhaps a combination of the two. Although the mechanism of action remains to be fully elucidated, experimental evidence suggests that celecoxib exhibits an anti-angiogenic activity and may induce cell cycle arrest and apoptosis in colon cancer cell lines. Further, epidemiological evidence suggests an association between the use of NSAIDs and a decrease in colon cancer in the general population. There is a strong association between the level of COX-2 expression in tumours and anticancer effects of COX-2 inhibition.

Celecoxib was evaluated in a series of nonclinical pharmacology studies: 1) to examine its inhibitory kinetics and mechanism of action; 2) to determine its anti-inflammatory, analgesic, antipyretic, and chemopreventative actions *in vivo*; and, 3) to specifically evaluate its propensity to cause GI tract injury and to explore its potential for action on a variety of physiological systems that are targets of conventional NSAIDs. A major goal of these studies was to understand the pharmacological action of celecoxib in relation to its ability to produce differential inhibition of COX isoforms *in vivo*, *ex vivo* and *in vitro*.

No new data regarding the anti-inflammatory and analgesic properties, and the general toxicity profile of celecoxib have been presented over and above the data submitted during the Mutual Recognition Procedure (MRP) for the OA and RA indication.

For the pharmacodynamic evaluation of the effect of celecoxib related to treatment of FAP, a chemical (AOM-induced ACF model) and a genetic (Apc Min mouse model) rodent model were used. These cancer models involve tumour types that are known to express COX-2 and are sensitive to conventional NSAIDs. In these models, distinct COX-2 expression occurs in the distal parts of the intestine.

The deletion of the COX-2 gene in the Apc mouse has been shown to reduce the size and number of intestinal polyps. A significant reduction in tumour formation has also been observed in COX-2 deficient mice with chemically induced skin papillomas, and in yet other cancer models COX-2 inhibitors such as sulindac have been shown to reduce the tumour burden. Evaluation of COX-2 mRNA and protein in the colon of Min mice parallel findings in human tumours, in which the majority of colorectal adenomas and adenocarcinomas express COX-2.

Celecoxib was shown to reduce the tumour burden in the Min mouse and the AOM rat models in a dose-dependant manner, in particular in the middle (jejunum, ileum (Min mouse)) and distal (colon (AOM rat)) parts of the intestine. Celecoxib effect was more marked in the early stage than in the late stage of carcinogenesis induced by AOM. However, these results do not support an extrapolation of the possible clinical effect on polyps in the colon and other intestinal segments expressing COX-2 to the rest of the gastrointestinal tract e.g. the duodenum.

It has been demonstrated that COX-2 expression in the uninvolved mucosa was 3- to 4 times higher in the distal as compared to the proximal bowel in both Min mice and AOM rats. The results from the studies in the Min mouse model also indicate that NSAIDs have distal predilection, at least partially. This finding may support the role of COX-2 inhibition as the major anticancer mechanism of NSAIDs. It has been reported that in 85% of colorectal adenocarcinomas taken from humans, COX-2 levels are 2- to 50-fold higher than levels in adjacent normal mucosa, and that COX-2 was over-expressed in polyps from FAP patients. However, the distinct intestinal distribution of effect (of celecoxib and other NSAIDs) in the Min mouse model, and its relation to COX-2 tumour expression distribution is important.

The pharmacodynamic effects of celecoxib against adenomas were observed at plasma concentration levels between 0.7 and 4.29 µg/ml. The preferential distribution of celecoxib to the gastrointestinal tract might perhaps result in an even higher concentration/exposure at the local target site of adenoma growth in FAP patients. In rats, the concentration of celecoxib in the large intestine from 1 to 8 hours post-dosing is 2- to 16-fold greater than the concentration in plasma.

The inhibitory effect of celecoxib on the Min-mouse model is comparable or sometimes lower than that of piroxicam, suggesting that the inhibitory effect on tumor multiplicity and/or volume is not specifically related to the expression of COX-2. Therefore, it is highlighted that the antitumorigenic effect of NSAIDs, COX-2 selective or not selective, might be related to the expression of both COX isoenzymes. Moreover the existence of COX-independent mechanisms by which NSAIDs exert their antitumorigenic effects, has been recently proposed.

The non-clinical safety evaluation was based on exposure to the test article. Plasma concentrations were measured in all toxicity studies and C_{max} and AUC_{0-24hr} were calculated. A comparison of the preclinical C_{max} and AUC_{0-24hr} values with the corresponding values obtained in human patients given celecoxib at 800 mg/kg is discussed.

The preclinical safety profile of celecoxib does not differ significantly from the earlier approved indications of osteoarthritis and rheumatoid arthritis, i.e. gastrointestinal toxicity and associated secondary toxicity. No main adverse findings were observed in safety pharmacology studies, but exposures were low.

In literature, it has been reported that COX-2 may play a critical role in the resistance to gastrointestinal tract injury following exposure to a mild irritant, and that blockage of COX-2 inhibited the defence mechanism. As a consequence, the COX-2 'selective' profile of celecoxib may raise a potential safety concern with regards to ulcer healing (retardation). The role of celecoxib's COX-1 inhibitory action at high exposure levels in the bleeding episodes observed in the clinical trials is uncertain in this context.

A full battery of genotoxicity studies has been performed. The overall evaluation of the results, under the conditions of the studies, suggests that celecoxib is devoid of a significant genotoxic activity. Further, celecoxib administered by gavage to rats or in the diet to mice did not show any indication of a treatment related increased risk of carcinogenicity. The assays were conducted according to ICH guidelines.

Reproduction toxicity studies have been conducted in male and female rats and rabbits. Celecoxib affects fertility due to the increased pre- and post-implantation losses seen in rat and rabbit, reduced gestation index and increased length of pregnancy in rat.

The results of rat and rabbit teratology studies suggest that Celecoxib acts as a teratogen in both species without any treatment-related clinical sign or change in body weight of dams. The induced diaphragmatic hernia is the same phenotype as occurred spontaneously in maternal animal, suggesting the presence of a genetic susceptibility background. This may represent a further concern for humans, due to the possible presence of enhanced susceptibilities within the population. Celecoxib is contraindicated in pregnancy, in women who can become pregnant unless using an effective method of contraception and in breast-feeding and this is sufficiently covered by the SPC and Package Leaflet.

4. Clinical aspects

Clinical pharmacology

Pharmacodynamics

It is generally accepted that colorectal cancer is preceded by adenomas. Large intervention studies have demonstrated that removing adenomas reduce the risk of developing colorectal cancer. Several clinical and epidemiological studies have demonstrated that extended periods of NSAID intake is associated with a 40-50% reduction in the incidence of colorectal cancer and a decreased risk of developing adenomas. Small and methodologically less optimal studies clearly indicate that the NSAID sulindac can reduce the number and size of polyps in patients with FAP. Treatment is, however, limited by the gastrointestinal side effects related mainly to the inhibition of COX-1.

A rapidly increasing pool of published experimental and human data indicates that COX-2 is involved in colorectal carcinogenesis. COX-2 is upregulated and overexpressed in adenomas and colorectal cancer also in FAP patients and related to tumour angiogenesis in human colorectal cancer. Polyps in FAP with the APC mutation overexpress COX-2 and left untreated, these polyps continue to form and enlarge in the colon or rectum resulting in essentially a 100% chance of developing colorectal cancer. Inhibition of COX-2 leads to inhibition of angiogenesis and tumour cell proliferation as well as the induction of apoptosis. Thus, COX-2 stimulation may be one important common step in the pathway leading to adenomas and colorectal cancer regardless of the underlying genetic defect and COX-2 inhibition may represent a significant therapeutic option in the prevention and/or regression of adenomatous polyps.

Celecoxib is an orally active selective inhibitor of cyclooxygenase-2 (COX-2). No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B₂ [TxB₂] formation) was observed in healthy volunteers at the FAP therapeutic dose of 400 mg BID.

A dose-dependent effect on TxB₂ formation has been observed after high doses of celecoxib. However, in small multiple dose studies in healthy subjects with 600 mg BID celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.

COX-2 is probably 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.

No specific pharmacodynamic studies related to the proposed indication have been conducted and pharmacodynamic data with celecoxib are limited to that generated by the preclinical studies (see preclinical discussion), and include evaluations in animal models of FAP and colon cancer (primary pharmacology); molecular, enzymatic, and biochemical characterizations of inhibition of COX-2 (primary pharmacology); evaluations in animal models of inflammation and analgesia (secondary pharmacology); and evaluation of potential side effects and ancillary pharmacological activity (secondary pharmacology).

Celecoxib inhibits tumour formation in preclinical models of colon cancer, which express COX-2, whether induced by chemical (rat AOM model) or genetic (MIN mouse model) mutation.

Some pharmacodynamic data can also be extrapolated from the clinical pharmacokinetics interaction studies, in particular those exploring the interaction between celecoxib and warfarin, glyburide and combined oral contraceptives (see discussion below). No clinically significant pharmacodynamic drug-drug interactions were observed in these studies.

Pharmacodynamic interaction studies

All pharmacodynamic drug-drug interaction assessments were made in conjunction with studies of pharmacokinetic interactions (see also section on pharmacokinetic interactions below).

In a warfarin interaction study investigating the pharmacodynamic and pharmacokinetic effects of celecoxib 200 mg BID, no significant differences in prothrombin time were seen during celecoxib treatment as compared to placebo. Anticoagulant activity should be monitored in patients taking warfarin or similar agents, particularly in the first few days after initiating or changing the dose of celecoxib. Bleeding events in association with increases in prothrombin time have been reported, in arthritis patients (mainly elderly) receiving celecoxib concurrently with warfarin, some of them fatal.

Another study investigated the effect of celecoxib on the glucose and insulin levels in type 2 diabetic patients receiving the oral hypoglycaemic agent glyburide (glibenclamide) 5 and 10 mg QD. There were no clinically relevant changes in glucose and insulin levels when celecoxib was administered compared to placebo.

There is no indication that celecoxib given to women under oral contraception would alter the efficacy of oral contraceptives.

Further, NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors are combined with celecoxib.

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

Celecoxib can be used with low dose acetylsalicylic acid, however it cannot be considered a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

Pharmacokinetics

Basic pharmacokinetics

Pharmacokinetic data were obtained from studies in young and elderly healthy subjects of both sexes as well as from the various patient populations studied in support of the previously approved OA and RA indications. Both single and multiple dose studies were performed but data are limited to administration via the oral route.

Celecoxib is a low solubility, high permeability substance with good oral bioavailability and low first-pass metabolism either in the gut or liver.

Celecoxib has a plasma CL/F of ~500 ml/min (30 L/hr/70 kg) adjusted for 70 kg body weight in young healthy adults. It has a protein binding in vivo of about 97% and this binding remains constant within wide therapeutic concentration range of the total drug. The apparent distribution volume (V_z/F) of celecoxib is ~500 L/70 kg after single 200 mg dose in young healthy adults, suggesting extensive tissue uptake. Celecoxib is absorbed after oral administration with t_{max} approximating 3 hours. Celecoxib half-life ($t_{1/2}$) is ~10-12 hr. Its absolute bioavailability is not known because of the unavailability of an intravenous dosage form. It is, however, estimated that at least 73% of the orally administered dose reached the systemic circulation. The apparent oral clearance was about 30 l/h, but with a high degree of variation.

The AUC of celecoxib increases less than proportional with dose when the dose exceeds 200 mg, especially at doses larger than 600 mg. This may be due to the low biopharmaceutical solubility resulting in dissolution-limited saturation in the absorption at high doses.

Celecoxib is extensively metabolised in man. The percentage of dose excreted in feces is only 2.6% and no unchanged drug was detected in urine. Both in vitro and in vivo studies indicate that this hydroxylation pathway is mediated predominantly via CYP P450 2C9. The important role of CYP2C9 was supported by clinical interaction studies. Three metabolites of celecoxib were observed, all of them pharmacologically inactive with respect to COX-1 and COX-2 inhibition. Renal excretion of unchanged celecoxib is negligible.

Body weight and hepatic impairment were shown to be the two most important covariates that had important effects on celecoxib CL/F. These findings are expected since celecoxib is eliminated mostly by hepatic metabolism and a decrease in hepatic function is likely to result in decreased metabolism. The effect of body weight results from the fact that CL/F is derived from the relationship $CL/F = \text{dose}/AUC$ and since the dose (expressed as mg/kg) is higher in subjects with significantly lower body weight, decreased CL/F should be expected in these subjects.

There is a genetic polymorphism of CYP2C9 and less than 1% of the population are poor metabolisers and have an enzyme with decreased activity. Patients known to be CYP2C9 poor metabolisers have not been specifically investigated by the applicant, and should be treated with caution.

Pharmacokinetics in the target population

No formal pharmacokinetic trial has been conducted in FAP patients. Plasma samples were taken for population PK analysis from the FAP patients included in the clinical phase II study IQ4-96-02-001. The celecoxib CL/F values in FAP patients were then compared with those in OA and RA patients.

The intended clinical dose (400 mg BID), at steady state, produces an AUC_{0-24h} of 31.8 $\mu\text{g/ml/h}$ and a C_{max} of approximately 2.38 $\mu\text{g/ml}$. Further, plasma levels as high as 16.3 $\mu\text{g/ml}$ have been observed in FAP patients (6.8-fold higher than the reference value (2.38 $\mu\text{g/ml}$)). It is noted that for the AO and RA indications (at lower dose levels) it has been reported that C_{max} was about 3.5 $\mu\text{g/ml}$ and AUC_{0-24h} was about 43 $\mu\text{g/ml/h}$. CL/F in FAP patients at steady-state (31.0 L/hr, N=52) is similar to the CL/F in RA and OA patients (34.7 L/hr, N=110).

No further accumulation of celecoxib plasma concentrations seems to occur in FAP patients from month 3 to month 6 of celecoxib treatment. In the FAP trial, the celecoxib CL/Fs in patients with intact colon (29.7 L/hr, N=18) were shown to be similar to CL/Fs in patients with partial colectomy (32.5 L/hr, N=32). No correlation was found between exposure (AUC) and efficacy (reduction in polyp number).

Special populations

Impairment of hepatic function clearly reduces clearance and increases exposure of celecoxib. The effect is clinically relevant at moderate severity, and celecoxib should not be administered in severe cases of hepatic impairment. Compared to subjects with normal hepatic function, patients with mild hepatic impairment had a mean increase in C_{max} of 53% and in AUC of 26% of celecoxib. When dosed at 200 mg per day the corresponding values in patients with moderate hepatic impairment were 41% and 146% respectively. The metabolic capacity in patients with mild to moderate impairment was best correlated to their albumin values. In FAP patients with moderate hepatic impairment (serum albumin of 25-35 g/l), the daily recommended dose of celecoxib should be reduced by 50%. Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

Celecoxib CL/F is not markedly reduced in patients with stable chronic renal dysfunction (GFR >34 ml/min/1.73 m²) and in patients with Type II non-insulin dependent diabetes mellitus (NIDDM). The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients since it is mainly eliminated by hepatic metabolism. There is little experience of celecoxib in renal impairment and therefore caution is advised when treating patients with renal impairment. Severe renal impairment is a contraindication to use.

Celecoxib has not yet been studied for use in pediatric patients below the age of 18. The pharmacokinetics in elderly subjects has not been specifically studied in FAP. In elderly healthy subjects, AUC and C_{max} values are higher (about 67% and 85%) compared to young healthy subjects. Celecoxib CL/F is lower [higher drug exposure (AUC)] in elderly women and in patients with moderate hepatic impairment. Reduction in CL/F in elderly females (>65 years), can be partly attributed to age and partly to their lower body weight. However, the decrease in CL/F in healthy elderly Caucasians is <40% compared to healthy Caucasians <50 years. The plasma concentration of celecoxib is approximately 100% increased in elderly women (>65 years.)

The pharmacokinetics of celecoxib in females and males are similar.

Data from several studies indicate that body weight adjusted oral clearance is lower in black subjects compared to Caucasians. In a study of elderly subjects, there is no clinically significant difference in pharmacokinetic parameters between black subjects and Caucasians.

Pharmacokinetic interaction studies

Potential drug-drug interactions with celecoxib were evaluated based on previous experience with currently available NSAIDs and their effect on other drugs that have a narrow therapeutic window. NSAIDs are known to decrease renal blood flow and may potentially affect drugs that are eliminated

mostly by the kidney, such as methotrexate and lithium. Furthermore, NSAIDs typically undergo extensive hepatic metabolism and have the potential to interact with other drugs that are metabolized by the liver, in particular by cytochrome P450 (CYP) 2C9 isozyme, such as warfarin, tolbutamide and phenytoin. NSAIDs are typically highly protein bound and have the potential to cause protein binding displacement and/or effect the clearance of other highly protein bound drugs, such as glyburide.

Administration of an antacid (aluminium-magnesium hydroxide) with celecoxib produces a slight reduction in celecoxib AUC and more pronounced decrease in C_{max} . Fluconazole (a CYP2D9 inhibitor) increases celecoxib AUC more than 2-fold and also significantly increases C_{max} . Celecoxib administered as 200 mg BID for seven days did not significantly affect the kinetics of methotrexate. Serum concentrations of lithium increased slightly (17%) but this increase is not considered clinically important. Multiple doses of celecoxib also showed no clinically important interactions with other substrates of 2C9 namely, S-warfarin, phenytoin, glyburide and tolbutamide. In vivo studies with paroxetine and dextromethorphan have indicated that celecoxib is not a strong inhibitor of CYP2D6. Furthermore, these studies demonstrated that celecoxib is not a substrate of CYP2D6 in vivo.

Administration of celecoxib with food (high fat breakfast) results in increased bioavailability (AUC(inf) increased between 7% and 11%, C_{max} between 39% and 62%).

Bioequivalence

A bioequivalency link has been established between the capsules used in phase III pivotal clinical trials and the proposed commercial formulation.

Clinical efficacy

Dose-response studies and main clinical studies

Dose response studies

Plasma levels of celecoxib that were effective in the animal cancer prevention models, supported by findings in controlled clinical trials of celecoxib in patients with OA and RA, guided dose selection for the pivotal study. It had been demonstrated that a total daily dose of 200 mg, administered as 100 mg BID or 200 mg as a single dose, provided significant reduction in joint pain as well as significant reduction in joint swelling in RA patients. Doses up to 400 mg BID were also well tolerated, with no evidence of dose-dependent adverse events in the arthritis studies. The recommended daily dose for RA is 200-400 mg taken in two divided doses.

No additional dose finding study was undertaken in FAP patients given the small size of the patient population. Instead dose comparison was carried out as a part of the pivotal study with doses chosen based on the preclinical and OA/RA data.

Two doses, 100 mg BID (lowest efficacious dose in OA/RA studies) and 400 mg BID (a safe dose in OA/RA studies and one providing exposure comparable to the efficacious dose in preclinical cancer prevention models) were selected.

Main clinical study (IQ4-99-06-001)

The pivotal FAP study has been conducted in compliance with GCP rules.

Description of the study

The pivotal phase II study, IQ4-99-06-001, was a randomised, double-blind, placebo controlled, three arm parallel group study with 6 months duration in patients with FAP. The study was conducted at two sites: one in the UK and one in the USA.

Eighty-one patients (75 with lower gastro-intestinal tract disease and 6 with exclusively duodenal lesions) and an additional 2 replacement patients, both with lower tract disease, were enrolled in the study adding up to a total of 83 patients.

FAP patients with gastrointestinal disease were eligible provided that they had at least five endoscopically assessable colonic or duodenal polyps (stage III or IV polyp burden according to Spigelman criteria) remaining after baseline endoscopy and polypectomy. The eligible patient population had a diagnosis of FAP based on the following criteria: more than 100 polyps, or more than 10 polyps and age over 40 years, or more than 25 polyps and age over 40 years and a characteristic family history which included one of the following: over 100 polyps in a first degree family member or more than 25 polyps in two relatives in two generations, including a first degree family member.

Patients to be recruited had to be between 18 and 65 years of age and had to be willing to abstain from use of NSAID including aspirin. Women of childbearing potential had to accept use of an adequate contraception. Exclusion criteria included anticipated colectomy within 8 months, hypersensitivity to NSAIDs or salicylates, use of NSAID for 6 (3) months prior to study entry, a history of gastroduodenal ulceration within the last year (patients with H. pylori associated peptic ulcer disease became eligible upon H. pylori eradication), history of invasive cancer within 5 years (resected Duke's A & B1 accepted), anaemia with a haemoglobin < 10.0 g/dl or a platelet count of < 100.000 per μ L or significantly elevated liver enzymes or creatinine.

The two centres included 42 and 41 patients between the age of 19 and 64 years representing >90% and 25%, respectively of patients in their respective registries. The 77 FAP patients with gastrointestinal disease were randomised 1:2:2 to placebo, celecoxib 100 mg and celecoxib 400 mg BID, respectively. The 6 patients with only duodenal disease were randomised 1:1:1 to placebo, celecoxib 100 mg and celecoxib 400 mg BID. Treatment duration was 6 months up to 200 days.

The treatment groups were similar except that patients given the high dose celecoxib were younger and weighed less (median weight 75 kg, 75 kg and 68 kg, respectively in the three groups). The treatment groups were similar for race and gender at baseline. Across treatment groups, 88% to 94% of the patients were Caucasian and 56-59% were male. For all patients, the age range was 19 to 64 years. The groups were statistically different ($p=0.013$) for age at baseline, with the placebo group being oldest (41.2 years), the celecoxib 100 mg BID group being slightly younger (39.5 years) and the celecoxib 400 mg BID group being youngest (33.0 years). A statistical analysis of the robustness of the primary efficacy outcome showed that difference in age among the groups did not affect the conclusions of the study. All treatment groups were similar with respect to height, weight, vital signs at baseline and colon status. All in all, 15 placebo patients, 32 celecoxib 100 mg BID and 30 celecoxib 400 mg BID were analysed.

Upper and lower gastrointestinal endoscopies were performed at baseline and at the end of the study. Pre-designated areas were to be videotaped, photographed and scored in detail. The area in the rectum with the highest polyp burden and one or two areas in the proximal colon were marked with India ink tattoo and biopsied at the follow-up examination. Baseline polyp counts were obtained after removal of the large polyps and the two colonic areas with the highest polyp burden were to be avoided and at least 5 unbiopsied polyps to be left. Laboratory evaluation was performed at entry and at months 1, 2 and 6. Structured interviews for symptom assessment were performed at week 2 and 4 and monthly thereafter. Quality of life was determined at baseline, at month 3 and 6 or at early termination using the SF-36 health survey, which includes multiple items within each of eight domains: physical functioning, role-physical, bodily health, general health, vitality, social functioning, role-emotional, and mental health. The changes from baseline to endpoint scores were analysed. Biopsies were obtained for biomarker analysis. Dietary assessments were conducted at baseline and at termination but these results were not included in the final report.

RESULTS

Primary efficacy variables

The primary efficacy parameter was the percent change in colorectal polyp number from baseline as compared to the observation at 6 months. The absolute polyp numbers were obtained as the sum of counts from still photos of each of the tattooed sites and predefined areas.

Five discontinued patients with no data beyond baseline were included in the ITT analysis by defining all changes for the primary efficacy parameter from baseline as 0%. A protocol amendment stated that treatment efficacy was to be based on comparison of high dose vs. placebo and low dose vs. placebo based on type I errors of 0.04 and 0.01, respectively. Supportive analyses included percent responders, percent change in total polyp burden, percent change in size and number of polyps in different anatomical regions of the lower gastrointestinal tract, and physicians' review of videotapes of the endoscopies (mean of five blinded examiners). A total of 77 patients had lower gastrointestinal tract disease and was included in the analysis.

Celecoxib, 400 mg BID for 6 months, reduced the number of colorectal polyps by 28.0%, mean polyp size by 4.9% and overall polyp burden (sum of polyp diameters) by 30.7% as compared to baseline. Compared to the mean decrease of 4.5% in the placebo group, the between treatment difference was statistically significant ($p=0.003$). The difference in percent change of polyp size did not reach statistical significance in the celecoxib 400 BID group compared to placebo. Compared to baseline, celecoxib 400 mg BID reduced the colorectal polyp burden by 30.7% on average and celecoxib 100 mg BID reduced the colorectal polyp burden by 14.6%. Compared with the mean reduction of 4.9% in the placebo group, this difference was statistically significant for the celecoxib 400 mg BID group ($p=0.001$). The latter analysis consists in practice in the sum of polyp diameters.

Variable	Selected Efficacy		
	ITT Population		
	Placebo BID	Celecoxib 100 mg BID	Celecoxib 400 mg BID
Number of Colorectal			
Baseline Mean	15.5 (15)	11.5 (32)	12.3 (30)
Mean % Change from Baseline at Month 6	-4.5 (15)	-11.9 (32)	-28.0 ^a (30)
Mean Residual Colorectal Polyp Size			
Baseline Mean	2.9 (15)	2.9 (32)	2.9 (30)
Mean % Change from Baseline at Month 6	-0.7 (15)	-3.0 (32)	-4.9 (30)
Mean Colorectal Polyp Burden (Sum of Polyp			
Baseline Mean	44.7 (15)	34.8 (32)	37.6 (30)
Mean % Change from Baseline at Month 6	-4.9 (15)	-14.6 (32)	-30.7 ^b (30)
Percent Area of Duodenum Covered By -Like Polyps			
Baseline Mean	16.2 (12)	12.8 (23)	8.8 (17)
Mean % Change from Baseline at Month 6	-1.4 (12)	117.9 (23) ^c	-14.5 (17)

- Statistical significance compared to placebo of $p=0.003$.
- Statistical significance compared to placebo of $p=0.001$
- Analysis of percent area of duodenum covered by plaque-like polyps, with two patients who had a zero percent coverage at baseline excluded, indicated a 4.2% reduction in the celecoxib 100 mg BID treatment group compared to placebo

Findings for the primary endpoint were also examined for progression or <10% reduction in number of colorectal polyps, >10% reduction in number of colorectal polyps, >25% reduction in number of colorectal polyps and >50% reduction in number of colorectal polyps. More patients in the celecoxib 400 BID than in the placebo group had a $\geq 50\%$ and a $\geq 25\%$ reduction in number of colorectal polyps compared to baseline:

	Placebo (N=15)	Celecoxib 100 mg BID (N=32)	Celecoxib 400 mg BID (N=30)
Progression or ≤10% reduction % (N)	73.3% (11)	56.2% (18)	26.7% (8)
>10% reduction % (N)	26.7% (4)	43.8% (14)	73.3% (22)
≥25% reduction* % (N)	6.7% (1)	31.2% (10)	53.3% (16)
≥ 50% reduction % (N)	0.0% (0)	9.4% (3)	16.7% (5)

* p=0.003 celecoxib 400 mg BID vs. placebo by Fisher's Exact Test; only percent responders based on 25% reduction was analyzed

Further, with reference to the overall number of polyps in each treatment group at baseline and at 6 months, along with the change from baseline, the reduction in total number of polyps was greatest for the celecoxib 400 mg BID group:

	Placebo	Celecoxib	
		100 mg BID	400 mg BID
N	15	32	30
Baseline	232	369	369
Final	213	344	264
Difference	-19	-25	-105
Change	-8.2%	-6.8%	-28.5%

Furthermore, a consistent improvement in the condition of the rectum and all colon regions was observed in patients in the celecoxib 400 mg BID treatment group compared to the placebo group, confirming findings for the percentage change in the number of polyps, percentage of responders, mean residual polyp size and polyp burden in this treatment group. Global assessments showed a statistically significant improvement in each colorectal segment for the celecoxib 400 mg BID treatment group when compared to the placebo group.

Secondary efficacy variables

The secondary efficacy parameter was the percent change from baseline in an area of the duodenum covered by plaque-like polyps. The absolute values were obtained by computing one high polyp density photograph and one low polyp density photograph. There were two patients without duodenal plaques at baseline and some duodenal plaques at the end of study for which the percent change was calculated assuming a baseline value of 1%. Supportive analyses included percent change in the size of the ampulla, the Spigelman grade (based on histology, dysplasia, size, and number of polyps) and the physicians' review of videotapes. The 52 patients included in the ITT analysis of the secondary parameter included the 6 patients with only plaque like duodenal polyps and 46 patients with measurable duodenal disease at baseline and study exit.

52 patients were available for evaluation of the secondary endpoint, which is more difficult from an endoscopic point of view. Celecoxib 400 mg BID reduced the area of the duodenum covered by plaque-like polyps by 14.5%, a reduction that did not reach statistical significance compared to the change in the placebo group (p=0.436). A trend towards a dose-dependant response was nevertheless noted (placebo 1.4%, celecoxib 100 mg BID 4.2% and celecoxib 400 mg BID 14.5%). However it has to be mentioned that two patients in the celecoxib 100 mg BID group had no plaque-like polyps at baseline and were excluded from the previous calculation. If these patients are included in the analysis, there is a 117.9% (p=0.986) increase in the area of duodenum covered by plaque-like polyps for the celecoxib 100 mg BID treatment group.

Results for global assessments of endoscopic videotapes by a blinded GI panel revealed an improvement considered statistically significant for the celecoxib 400 mg BID treatment group.

Clinical studies in special populations

No studies in special patient groups (e.g. in children) were performed.

Discussion on clinical efficacy

No specific pharmacodynamic studies related to the proposed indication have been conducted, however, there is evidence that elevated levels of COX-2 are found in several types of tumours, including colon, as well as in pre-cancerous conditions such as adenomatous polyps. Human and experimental colon tumours contain increased amounts of prostaglandin E2, which is thought to participate in colon cancer carcinogenesis. COX-2 appears to be responsible for increased prostaglandin E2 levels in response to growth factors in human and animal colonic tumours. COX-2 inhibition may therefore play an important role in colon cancer prevention. More recent data indicate that NSAIDs increase apoptosis, inhibit angiogenesis, and reduce metastasis in various experimental models of carcinogenesis.

Circumstantial evidence that the inducible isoform of COX contributes to colorectal neoplasia is that COX-2 is up-regulated as normal intestinal mucosa progresses to invasive colorectal cancer in humans.

Published data also indicate that inhibition of COX-2 leads to inhibition of angiogenesis, tumour cell proliferation and the induction of apoptosis. This mechanism may play an important role in the prevention and/or regression of adenomatous polyps. Overall, the rationale for the development of celecoxib is considered sound and the lack of specific studies acceptable.

The application is based on one single study on efficacy and safety in the target population and supportive safety studies in different patient groups. The pivotal phase II study was a randomised double-blind placebo controlled study conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

However, despite the achievement of a large study group of 83 FAP patients in the study performed, there remains concern as to whether the study population is truly representative of the general FAP population. Differences between the study arms with reference to age and number of polyps at baseline were noted. Patients on the high dose of celecoxib were younger and the baseline number of colorectal polyps was largest in the placebo group.

Celecoxib 400 mg BID has shown some efficacy in comparison to placebo with regard to the percent reduction in the number of colorectal polyps in patients with FAP. Celecoxib has been shown to reduce the number and size of adenomatous colorectal polyps. However, the 28% change from baseline in the number of colorectal polyps (the primary efficacy endpoint) measured in the FAP patients treated with celecoxib 400 mg BID was lower than the prespecified 40% difference for which the study was powered and which was considered a clinically relevant difference and in line with previous studies of NSAIDs. The reduction in polyps observed with celecoxib 400 mg BID was statistically superior to placebo at the six-month time point. The net difference with placebo is 23.5%, which is also not very convincing. Moreover, percentages are highly influenced by the relatively small absolute numbers of the study. In terms of absolute numbers, 7 out of 30 patients in the celecoxib 400 mg BID group did not show any reduction in polyp number (in two of them it even increased), corresponding to a percentage of 23.3%. Similarly, with reference to the number of polyps, 369 polyps at baseline in 30 patients (mean: 12.3) were reduced to 264 after six months (-105, mean: 3.5). The maximum number of polyps found in an individual patient at baseline was 41 while the vast majority of patients had much less than 20 polyps. Even though a small reduction in polyp number might possibly be translated into an absolute reduction of the risk of developing cancer, it is not clear how such a reduction would change the clinical approach to the disease and thus whether the findings are clinically relevant.

Although it is recognised that the duodenal assessment is harder than the colorectal one, and the accuracy of the adopted techniques of a poorer standard, the results are at best considered encouraging. Moreover, the preclinical rationale for the duodenal disease is to be considered weak.

Extensive duodenal disease, i.e. Spigelman IV is associated with a high (36%) risk of developing cancer and (prophylactic) treatment is a radical and mutilating Whipple operation. Demonstration of a convincing effect on the duodenal manifestation of FAP would be of more crucial value for the long-term treatment than an effect on colonic disease for which the surgical treatment is much less mutilating. Unfortunately, however, the applicant chose to assess the effect of celecoxib on duodenal disease as a secondary parameter and to perform a much less rigorous study than that on colonic disease.

Results of the videotape assessment from study FAP-001, however, show a clinical improvement ranging from 16.5 to 25% in the duodenum in patients receiving the 400 mg BD dose.

Regression of large plaque-like adenomas does not occur uniformly, therefore, counting adenoma number, as is done for colorectal adenomas, is not a technique amenable to assessment of duodenal adenomas. However, the assessment of duodenal plaque area does show a reduction in plaque area of 14.5% in patients treated with Onsenal 400 mg BD vs. 1.4 % in placebo, demonstrating consistency with the results seen in the video assessment. Although not statistically significant, these results may be considered supportive for an effect in the duodenum, which was not, on the other hand, the primary objective of the pivotal trial.

Reducing the number, or eliminating adenomas, is the primary goal of all therapeutic interventions in FAP. Multiple published studies have demonstrated a correlation between the number of adenomatous polyps and the risk of rectal cancer in FAP patients even after partial colorectal surgery. Although these studies vary in design, number of patients, and the years of follow-up, the conclusions are robust and derive their strength from the consistency of these findings among multiple centers and studies. The development of rectal cancer is a highly significant risk in any remaining mucosa in FAP patients, and while a prospective study demonstrating that untreated adenomas develop into cancer would be ideal, this would not be ethical given the availability of subsequent surgical options.

Despite a similar reduction in polyp size and number as previously demonstrated with sulindac, NSAID therapy has not become part of the standard of care in FAP patients because of substantial uncertainty on the balance between potential benefits and risks. Such an uncertainty remains also for celecoxib, because of the limitations outlined above regarding efficacy, and because of safety concerns identified (see discussion on safety below). In fact, also measurement of quality of life of treated patients did not reveal any statistically significant improvement as compared to placebo.

In summary, independent assessment of both colorectal adenomas and duodenal adenomas, using site-appropriate measurement techniques is suggestive of a certain clinical benefit of celecoxib 400 mg BD in the treatment of FAP. The colonic efficacy findings appear robust although the absolute magnitude of polyp reduction was not overwhelming. The number of polyps decreased in all groups including placebo. It remains, however, to be shown that this reduction was clinically relevant, i.e. either that the natural history of FAP with adenomas developing into adenocarcinomas was changed or that the therapeutic approach could be modified. Since it is not anticipated that the presented data will persuade clinicians to postpone colectomy the answer must come from analysis of patients in which a colectomy or proctocolectomy had previously been performed, i.e. in patients with remnant rectal mucosa, duodenal disease or desmoids. In fact, although celecoxib did reduce the mean number of polyps in the rectum from 11 to 8 in accordance with the overall result this effect was not statistically different from the reduction from 17 to 15 in the placebo group. The difference in baseline number of polyps was significant. The small effect of celecoxib will probably not change the surgical approach towards the colorectal disease in patients with FAP. Whether it will change the handling of disease in the remnant rectum remains to be demonstrated. It is not known whether the effect on colonic polyps can be extrapolated to other parts of the gastrointestinal tract, in particular to the duodenum, the mucosa of which differs significantly from colon.

It is acknowledged that the reduction of adenomatous polyps in FAP patients does not provide a cure for patients with FAP. In relevant settings, however, Onsenal might provide a benefit to patients specifically in conjunction with routine surveillance thus enhancing the management of FAP patients. Surgery could be an aggravating factor and the usefulness of a pharmacological tool should be taken in

consideration in this subset of severely ill patients. Whether long-term treatment with celecoxib may allow for a delay in colon surgery and possibly a reduction in the life-long risk of cancer in FAP patients remains to be established. The primary end-point of the pivotal efficacy study was the % reduction in colorectal polyp numbers. These results seem to support the claimed indication, but the clinical relevance of the outcomes is still far to be demonstrated.

Treatment with celecoxib in FAP has been studied for up to 6 months and has not been shown to reduce the risk of gastrointestinal or other form of cancer or the need for surgery. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and FAP-related surgery should not be delayed.

Since the prospective analysis was limited to 6 months, careful post-marketing surveillance will be required and the Applicant has committed to provide further longer-term safety and efficacy data for Onsena as part of a post-marketing programme.

Clinical safety

Patient exposure

In addition to the pivotal phase II study including 83 FAP patients, further safety data were derived from studies in the OA/RA indication at 400 mg BID and from the post-marketing setting including the most recent Periodic Safety Update Reports (PSURs). Overall 615 patients received celecoxib at the recommended dose for the FAP indication in the 4 placebo-controlled arthritis studies for duration of 4 or 12 weeks. There is supportive data from an open-label long-term safety study in 1630 patients with OA or RA and the class study including 3987 patients with OA or RA (see discussion below).

Phase II/III studies with celecoxib 400 mg BID in the OA/RA indication:

INDICATION	STUDY DESIGN	# Patients treated at 400 mg BID	TREATMENT DURATION
OA	Phase II dose-range study	99	4 weeks
RA	Phase II dose-range study	82	4 weeks
RA	Phase III, randomised, double-blind, placebo-controlled	217	12 weeks
RA	Phase III, randomised, double-blind, placebo-controlled	217	12 weeks
OA,RA	Open-label, long-term safety study	1630	12-24 weeks
OA, RA (CLASS study)	Phase III, double-blind parallel group, long term safety study	3987	26-65 weeks

Adverse events and serious adverse events/ deaths

FAP:

In the pivotal phase II study in FAP patients, 79 (95%) of the 83 patients receiving at least one dose of the study drug reported one or more treatment-emergent adverse events during the study. Adverse events were reported by 16 (94%) of the patients receiving placebo; 32 (94%) of the patients receiving celecoxib 100 mg BID; and 31 (97%) of the patients receiving celecoxib 400 mg BID. Both doses of celecoxib were well tolerated as compared to placebo. The most commonly reported adverse events were diarrhoea, dyspepsia, fatigue, blood per rectum (rectal spotting), upper respiratory infection and rash (see table below).

Adverse event	Placebo (n=17)	Celecoxib 100 mg BID (n=34)	Celecoxib 400 mg BID (n=32)
Diarrhea	6 (35.3%)	11 (32.4%)	14 (43.8%)
Dyspepsia*	5 (29.4%)	9 (26.5%)	11 (34.4%)
Fatigue	8 (47.1%)	6 (17.6%)	10 (31.3%)
Blood Per Rectum	2 (11.8%)	3 (8.8%)	10 (31.3%)
URTI	6 (35.3%)	13 (38.2%)	9 (28.1%)
Rash	3 (17.6%)	1 (2.9%)	9 (28.1%)

*All patients with negative endoscopy at end of study

Overall, the types of side effects of celecoxib reported in the FAP population were similar to those observed in the arthritis population. Intestinal surgical anastomotic ulceration was the only adverse event reported by celecoxib-treated patients in the FAP trial that was not reported in the arthritis studies. This was observed in 3 of 58 patients who had prior intestinal surgery before entering the FAP study. Pre-existing ulcers localised to the ileal anastomosis worsened in two patients and had developed in a third patient at the end of study; all were on celecoxib.

Patients on celecoxib 400 mg BID reported blood per rectum more frequently than those in the placebo group (P=0.175). However, a thorough analysis of these patients revealed no association to treatment or several other factors and concluded that the bleedings were neither statistically nor clinically significant when compared with the placebo group. 22% of the patients reported previous rectal spotting upon entering the study. One patient on celecoxib 100 mg BID experienced severe anaemia and haemoglobin decreased by at least 1 g/dL in approximately 10% of patients in each treatment group.

The upper gastrointestinal endoscopies performed at baseline and at the final visit revealed no cases of gastritis, inflammation or ulceration.

Three patients experienced severe adverse events. One patient with known psychiatric illness committed suicide, one had an elective resection of pre-existing angiofibroma and continued in the study, and one experienced an allergic reaction to celecoxib in the form of a bronchospasm treated with oral medication.

There were no statistically significant changes in health-related quality of life in patients with FAP who had been treated for 6 months with either celecoxib 100 mg BID or celecoxib 400 mg BID when compared to those treated with placebo.

OA/RA:

The following reactions were commonly observed (>1%) in arthritis patients receiving celecoxib in clinical trials:

Cardiac disorders: peripheral oedema; Renal and urinary disorders: fluid retention; Gastrointestinal disorders: abdominal pain, diarrhoea, dyspepsia, flatulence; Nervous system disorders: dizziness; Psychiatric disorders: insomnia; Respiratory, thoracic and mediastinal disorders: pharyngitis, rhinitis, sinusitis, upper respiratory tract infection; Skin and subcutaneous tissue disorders: rash.

The CLASS study combined two arthritis protocols which compared the incidence of “clinically significant upper gastrointestinal events” (e.g. perforation, gastric outlet obstruction, and bleeding), and “gastroduodenal ulcers” associated with celecoxib 400 mg BID to those associated with ibuprofen 800 mg TID and diclofenac 75 mg BID in patients with RA or OA.

In this multicentre, double-blind study 3987 patients received celecoxib and almost 2000 patients received each NSAID comparator, making up a total of 8059 patients. All patients were provided an opportunity to complete a minimum of 6 months of treatment. The planned analysis of the entire cohort at 6 months showed a lower incidence of combined clinical upper GI events for celecoxib than the comparator NSAIDs. The analysis for the entire study period showed that the safety difference between celecoxib and pooled NSAIDs for “clinically significant upper gastrointestinal events” was not statistically significant, while considering the combined end point of “clinically significant upper

gastrointestinal events” and “gastroduodenal ulcers”, an improved safety profile of celecoxib was seen and the difference between celecoxib and pooled NSAIDs became statistically significant (1.85% vs. 2.81%). The CLASS study showed no difference in the incidence of overall cardiovascular events and no difference in the rate of myocardial infarction among treatment groups. In the CLASS study celecoxib 400 mg BID was associated with a lower rate of chronic GI blood loss causing anemia, and GI adverse events than diclofenac and ibuprofen administered at conventional doses for OA and RA.

The most common adverse events observed in the CLASS study were dyspepsia (17%), upper respiratory tract infection (15%), headache (14%), abdominal pain (12%), and diarrhoea (11%). The majority of events occurred within the first 3 months of treatment and the events occurring later were similar in character to those occurring early. A gastrointestinal adverse event was encountered by 46% of the patients and 12% of participating patients withdrew due to gastrointestinal adverse event, i.e. 26% of patients experiencing a gastrointestinal adverse event withdrew as a result. A rash was seen in 247 patients (6%) causing withdrawal in 85 (2%) and pruritus occurred in 97 (2%) causing withdrawal in 29 (1%). A risk factor analysis identified for celecoxib was advanced age (>75 years), history of cardiovascular disease and low dose aspirin use but not a history of upper gastrointestinal bleeding or ulcer.

The major serious adverse events observed in the CLASS study were cardiac events (79), gastrointestinal (13), infection (22) and syncope (5). Nineteen deaths (cardiac 11, infection 3) occurred during or after the study, none of which resulted from a gastrointestinal cause or were judged to be related to the use of celecoxib.

A small decrease was noted in platelet count and was not seen in the other NSAID arms of the study. Neither ferritin, haemoglobin nor haematocrit decreased. Creatinine levels increased slightly. A decrease of haemoglobin in excess of 2 g/dL and/or a drop in haematocrit of 0.10 or more was registered in 87 patients (2.4%) of which 50 completed the study and 12 withdrew due to gastrointestinal disease.

Post marketing experience

Since its first market launch in December 1998, an extensive number of patients have been treated with celecoxib for arthritis outside of clinical trials. An assessment of the safety profile must therefore consider also the spontaneous reports by health professionals or health authorities, or from medical literature, as presented in the Periodic Safety Update Report (PSUR).

Post marketing surveillance

Study N49-01-06-024 was an open label multicenter study of the long-term safety of celecoxib. A total of 5157 patients with osteoarthritis (2920) or rheumatoid arthritis (2237) originally included in double blind studies of celecoxib entered the study and 2660 completed it. The mean age was 59 years with a range of 21-90 years. The mean weight was 80 kg for females and 93 kg for males. The initial dose of celecoxib of 100 and 200 mg BID, respectively, could be increased or decreased as necessary to a maximum of 200 and 400 mg BID in patients with osteoarthritis and rheumatoid arthritis, respectively. Almost none of the patients with osteoarthritis were given the 400 mg BID dose while half with rheumatoid arthritis received 400 mg BID for shorter or longer periods of time giving a total of 1436 patient years exposure. Participants were evaluated at least every 3 months. A subset of patients (1620) continued in the study after a protocol amendment had terminated data capture with the exception of severe adverse events at 24 months. Duration of treatment included exposure time in the primary randomised studies.

Adverse events were reported by 4445 patients (86%) and were considered to be attributable to the study drug in 420 patients (8%). The most common adverse events were upper respiratory tract infections (22%), headache (18%), dyspepsia (13%), sinusitis (13%), accidental injury (12%), diarrhoea (10%), abdominal pain (8%), nausea (7%), bronchitis (7%), back pain (7%), peripheral oedema (6%), dizziness (6%), coughing (6%), influenza like symptoms (5%), insomnia (5%) urinary tract infection (5%), and rhinitis (5%). During the entire study period 666 patients (13%) withdrew

due to adverse events. A total of 210 patients (4%) withdrew due to gastrointestinal adverse events including abdominal pain, dyspepsia, gastroduodenal ulcers, diarrhoea, and nausea. Rash led to withdrawal of 33 patients (<1%).

A total of 685 patients (13%) reported 974 serious adverse events. The rate of events per 100 patient years was 10% without significant differences between dosages. When stated as incidence as percentage of 100 patient years the most common serious adverse events were related to the body as a whole (1.4%; back pain: 0.5%), gastrointestinal tract (1.3%), ischemic cardiac disorders (1.2%), and respiratory disease (0.9%; pneumonia: 0.4%).

Twenty-nine out of a total of 41 deaths occurred in or within 28 days of discontinuation of treatment. None of the deaths were considered to be related to celecoxib. There were 22 deaths from cardiovascular causes, 6 from neoplasms and 5 due to serious infectious diseases.

Periodic Safety Update Reports

In the latest PSUR, the cumulative patient exposure is estimated from the sales volume. Since December 1998, 21.5 million patients are estimated to have been exposed to celecoxib based on an average daily dose of 200 mg and a 6 month-treatment period per patient. From a qualitative and quantitative evaluation of the current and previous PSURs it is considered that overall the safety information deriving from spontaneous reports is consistent with the drug profile as characterised in the arthritis clinical trials.

Reports from post-marketing experience in patients with OA/RA include headache, nausea and arthralgia, also the following very rare <1/10,000 and isolated reports:

Allergic reactions: serious allergic reactions, anaphylactic shock, angioedema; Blood and the lymphatic system disorders: pancytopenia; Cardiac disorders: heart failure, myocardial infarction; Gastrointestinal disorders: gastrointestinal haemorrhage, acute pancreatitis; Immune system disorders: vasculitis, myositis; Hepato-biliary disorders: hepatitis, jaundice; Psychiatric disorders: confusion, hallucinations; Renal and urinary disorders: acute renal failure; Respiratory, thoracic and mediastinal disorders: bronchospasm; Skin and subcutaneous tissue disorders: isolated reports of skin exfoliation including: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme.

The last periodic safety update covers January through June 2001. During this period the sales were 922,000,000 200 mg capsules and 203,000,000 100 mg capsules. The number of patients exposed was calculated assuming an exposure of 6 months per patient. Approximately 15,000 patients were exposed in clinical trials.

With regard to spontaneous reports no new safety concerns were identified. The most frequently reported events were dermatitis (384), rash (201), gastrointestinal haemorrhage (236), abdominal pain (182), oedema (169), pruritus (165), urticaria (154), hypersensitivity (118), diarrhoea (112). All of these reactions are already listed in the SPC.

Serious adverse event reported during clinical trials were planned surgery (73), malignancies (66), gastrointestinal bleeds (51), myocardial infarction (42), arthritis (41), back pain (32), abdominal pain (31), accidental injury (29), cerebral vascular disorders (28), and cardiac failure (26). These events are either listed in the SPC or frequently occurring in the patient population treated.

No new interactions were identified.

Discussion on clinical safety

Safety data in patients with FAP are limited. The only pivotal clinical trial which is part of the submitted documentation does not allow for any firm conclusions with reference to safety of celecoxib 400 mg BID in patients with FAP. Observation time is very short in comparison with the anticipated life-long treatment of patients with FAP. The small sample size is insufficient to draw any conclusion and to allow for a proper assessment of differences with reference to serious adverse events between celecoxib and placebo and to gastrointestinal safety. Generally, celecoxib was well tolerated in FAP patients and neither incidence nor character of adverse events differed statistically significantly between placebo and celecoxib groups. However, the observations of intestinal anastomotic

ulcerations are worrying and together with the trend towards more frequent episodes of blood per rectum in patients on celecoxib 400 mg BID they raise concern. Although a thorough analysis of the available safety data has been performed, long-term safety with the high dosage in the intended target population has not been proven and treatment should probably be discontinued for a considerable time in relation to surgery.

Safety data from studies in patients with other conditions than FAP are submitted as supportive evidence. In two large safety studies in patients with rheumatoid arthritis or osteoarthritis, 3987 and 5157 patients, respectively, received celecoxib in doses of up to 400 mg BID for up to 30 months. The data from these studies indicate that the use of high doses of celecoxib is associated with definite adverse events but no new safety issues were detected. There is no evidence of cumulative toxicity with prolonged use. Celecoxib does induce injury in gastrointestinal tract and increase the incidence of blood per rectum. Compared with the FAP patients these data relate to a much older population with more risk factors. In this respect the results are reassuring.

Furthermore, in order to further support long-term safety, the applicant provided a complementary analysis presented as a cohort, age-matched to the FAP cohort. The new analysis was performed at 90-day intervals and shows an absence of cumulative GI and CV risk in patients receiving celecoxib 400 mg BD for up to one year. However, these data are in arthritis patients and may not be directly comparable to FAP patients. In addition, the applicant confirms that two separate, independent Data Safety Monitoring Boards in their review of ongoing placebo-controlled trials of celecoxib in patients with SAP reported no safety concerns after 1 year. This provides additional supportive evidence for the long-term safety of Onsenal. Because of the limited number of patients with FAP, long-term data in a large population of FAP patients cannot be expected. Given the risk setting for FAP disease, the growing evidence of long-term safety in arthritis and SAP patients provides support for a similar risk profile in FAP patients at 400 mg BD. No useful information derives on the other hand from the age stratification related to patients <56 years not on aspirin.

The reported incidence of anastomotic ulcerations in the FAP-001 trial (5.2%) is similar to that reported at St. Mark's hospital during routine surveillance (6.4%). These data are reassuring, even if it is not known how many of these patients did in fact receive NSAIDs. However, in view of the fact that all surgical patients are given NSAIDs postsurgery when their anastomoses are most vulnerable this issue can be considered resolved as far as the FAP study is concerned. Furthermore, photographs of anastomotic ulcerations presented by the applicant indicate that these lesions are minor and do not appear to be clinically significant.

However, caution should be observed in patients with a history of gastrointestinal ulceration and related inflammatory conditions or in patients at special risk. Most spontaneous reports of fatal gastrointestinal events have been in elderly or debilitated patients. If an anastomotic ulcer is present, patients should not receive concomitant treatment with anticoagulants or acetyl salicylic acid.

In general the drug appears safe and well tolerated, but the claimed superiority as compared to conventional NSAIDs remains to be established, at least with the proposed doses. Celecoxib at 400 mg BID has not been shown to be significantly better than conventional NSAIDs in terms of serious upper gastrointestinal (GI) complications.

The authors of the CLASS study conclude that celecoxib at supratherapeutic dosages was associated with a lower incidence of symptomatic ulcers and ulcer complications than the comparator NSAIDs given at standard dosages. However, even though the combined incidence of symptomatic ulcers or POBs associated with celecoxib was significantly lower than with the comparator drugs, careful examination of the data shows that the rate of ulcer complications alone, the primary end point of the study, was not.

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

In the event of elderly patients with mild to moderate cardiac dysfunction requiring therapy, special care and follow up is warranted.

In patients on concurrent therapy with warfarin or similar agents, serious bleeding events have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulant activity should be monitored after initiating treatment with celecoxib or changing the dose.

Experience with celecoxib in patients with mild or moderate renal or hepatic impairment is limited, therefore such patients should be treated with caution.

The safety issues identified have been appropriately addressed in the SPC and Package Leaflet. However, since the prospective analysis was limited to 6 months, careful post-marketing surveillance will be required and the Applicant has committed to provide further longer-term safety and efficacy data for Onsenal as part of a post-marketing programme.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit/Risk balance of the product.

Preclinical pharmacology and toxicology

The pharmacodynamic rationale for celecoxib in FAP is its COX-2 inhibitor effect, possibly its molecular configuration independently of its COX-2 inhibition, or perhaps a combination of the two. For the pharmacodynamic evaluation of the effect of celecoxib related to treatment of FAP, a chemical (AOM-induced ACF model) and a genetic (Apc Min-mouse model) rodent model were used. These cancer models involve tumour types that are known to express COX-2 and are sensitive to conventional NSAIDs. Celecoxib was shown to reduce the tumour burden in the Min mouse and the AOM rat models in a dose-dependant manner, in particular in the middle (jejunum, ileum (Min mouse)) and distal (colon (AOM rat)) parts of the intestine. However, these results do not support an extrapolation of the possible clinical effect on polyps in the colon and other intestinal segments expressing COX-2 to the rest of the gastrointestinal tract e.g. the duodenum.

The preclinical safety profile of celecoxib does not differ significantly from the earlier approved indications of osteoarthritis and rheumatoid arthritis, i.e. gastrointestinal toxicity and associated secondary toxicity. No main adverse findings were observed in safety pharmacology studies, but exposures were low.

The results of rat and rabbit teratology studies suggest that Celecoxib acts as a teratogen in both species without any treatment-related clinical sign or change in body weight of dams. The induced diaphragmatic hernia is the same phenotype as occurred spontaneously in maternal animal, suggesting the presence of a genetic susceptibility background.

Celecoxib is contraindicated in pregnancy, in women who can become pregnant unless using an effective method of contraception and in breast-feeding and this is sufficiently covered by the SPC and Package Leaflet.

Efficacy

Familial Adenomatous Polyposis (FAP) is a genetic disease resulting from an autosomal dominant genetic alteration of a tumor suppressor gene, the adenomatous polyposis coli (APC) gene. Polyps with the APC mutation overexpress COX-2 and left untreated, these polyps continue to form and enlarge in the colon or rectum resulting in essentially a 100% chance of developing colorectal cancer. Celecoxib is an orally active selective inhibitor of cyclooxygenase-2 (COX-2).

Experimental evidence shows that the mechanism(s) of action by which celecoxib leads to tumour death may be related to induction of apoptosis and inhibition of angiogenesis. Inhibition of COX-2 may have consequences on tumour viability that are unrelated to inflammation.

Celecoxib has been shown to reduce the number and size of adenomatous colorectal polyps. A randomized double-blind placebo controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype. The mean reduction in the number of colorectal polyps following six months of treatment was 28% (SD \pm 24%) for celecoxib 400 mg BID which was statistically superior to placebo (mean 5%, SD \pm 16%) for placebo (p=0.003). The reduction in polyps observed with celecoxib 400 mg BID was statistically superior to placebo at the six-month time point.

A reduction in duodenal adenoma area was also observed compared with placebo (14.5% celecoxib 400 mg BID versus 1.4% placebo), which however was not statistically significant.

Surgery could be an aggravating factor and the usefulness of a pharmacological tool should be taken in consideration in this subset of severely ill patients. Whether long-term treatment with celecoxib may allow for a delay in colon surgery and possibly a reduction in the life-long risk of cancer in FAP patients remains to be established. The primary end-point of the pivotal efficacy study was the % reduction in colorectal polyp numbers. The approved indication is therefore *“for the reduction of the number of adenomatous intestinal polyps in Familial Adenomatous Polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated.”*

Treatment with celecoxib in FAP has been studied for up to 6 months and has not been shown to reduce the risk of gastrointestinal or other form of cancer or the need for surgery. The usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and FAP-related surgery should not be delayed. Careful post-marketing surveillance will be required and the Applicant has committed to provide further longer-term safety and efficacy data for Onsenal as part of a post-marketing programme.

Safety

Safety data in patients with FAP are limited. The only pivotal clinical trial which is part of the submitted documentation does not allow for any firm conclusions with reference to safety of celecoxib 400 mg BID in patients with FAP. Observation time is very short in comparison with the anticipated life-long treatment of patients with FAP. The small sample size is insufficient to conclude on potential differences in the frequency of serious adverse events between celecoxib and placebo and on gastrointestinal safety.

Generally, celecoxib was well tolerated in FAP patients and neither incidence nor character of adverse events differed statistically significantly between placebo and celecoxib groups. However, the observations of intestinal anastomotic ulcerations are worrying and together with the trend towards more frequent episodes of blood per rectum in patients on celecoxib 400 mg BID they raise concern. Although a thorough analysis of the available safety data has been performed, long-term safety with the high dosage in the intended target population has not been proven and treatment should probably be discontinued for a considerable time in relation to surgery.

In general the drug appears safe and well tolerated, but the claimed superiority as compared to conventional NSAIDs remains to be established, at least with the proposed doses. Celecoxib at 400 mg BID has not been shown to be significantly better than conventional NSAIDs in terms of serious upper gastrointestinal (GI) complications.

The safety issues identified have been appropriately addressed in the SPC and Package Leaflet. However, since the prospective analysis was limited to 6 months, careful post-marketing surveillance will be required and the Applicant has committed to provide further longer-term safety and efficacy data for Onsenal as part of a post-marketing programme.

Benefit/risk assessment

Following the assessment of the supplementary documentation provided by the Applicant, a number of key issues regarding clinical aspects of Onsenal treatment were identified that needed to be addressed at an Oral Explanation before the CPMP:

1. The clinical relevance of the set of submitted data remains controversial and should be further addressed by the Applicant with reference to the predictive value of a reduced number of polyps (primary endpoint of the pivotal trial) for the risk of rectal and duodenal cancer.
2. Polyp regression during COX-2 inhibitor therapy is unlikely to be a random phenomenon. It is therefore foreseen that selection of resistant polyps will occur. This view appears to be supported by the results of the long-term prophylaxis study by Giardiello et al. (NEJM 2002) and their treatment study (NEJM 1993) where there seems to be a loss of activity over time. The Applicant is therefore requested to discuss whether there are any non-clinical or clinical data addressing the risk for cancer development in polyps showing a COX-2 resistant phenotype compared with sensitive polyps.
3. In spite of the efforts made by the Applicant, the quality of data is not fully satisfying. The Applicant should further address the lack of data on intra-observer variation as well as the large inter-observer variation. Risk of unblinding, especially during the duodenal assessment, should be discussed.
4. The Applicant should address the long-term safety in FAP patients, related to both gastrointestinal complications and increased cardiovascular risk.

During this hearing, the Applicant concluded that FAP patients have limited therapeutic options and an unmet medical need exists for treatments that supplement the surgical management. Unfortunately, there is no evidence to suggest that celecoxib reduces the overall risk of colon cancer in this setting. Moreover, the allegedly improved gastrointestinal safety of celecoxib 400 mg bid vs traditional NSAIDs was not confirmed by the CLASS trial as reflected by lack of statistical significance of the difference in the primary end-point of the study.

The Applicant outlined the rationale for use of Onsenal, stressing that surgery is the appropriate standard of care and that Onsenal was not expected to change or replace surgical management or to eliminate cancer. The current treatment options were reviewed and the trial aim and end points of the FAP 001 trial described. The company also addressed, during the oral explanation, the long-term safety in FAP patients, the possible resistance to celecoxib and the ongoing studies to assess long-term effects of celecoxib use over time.

In response to questions from the Committee, the company clarified that pharmacological intervention was not seen as the treatment of choice, but could be used, together with advanced endoscopic methods, following primary surgery, thereby possibly delaying the time to more radical surgical intervention. It was also noted that studies to assess time to more aggressive surgery or to determine clinically relevant endpoints were not being considered in view of the ethical issues such studies raised (re cancer growth and possible delay in surgery). With respect to when treatment would be stopped, it was clarified that treatment would be maintained as long as there was a continuous depression in polyps but would be stopped in the event of an increase in polyp number.

The CPMP considered that Onsenal might be of benefit in patients who had already undergone primary surgery and with residual disease and who are treated at specialised centres. While Onsenal was not seen as a substitute for surgical intervention and the impact of the treatment on cancer risk and on the need and timing of secondary surgical intervention was unknown, the product did appear to be of benefit to a proportion of patients in reducing polyp burden.

Treatment with celecoxib in FAP has been studied for up to 6 months and has not been shown to reduce the risk of gastrointestinal or other form of cancer or the need for surgery. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In

particular, the frequency of routine endoscopic surveillance should not be decreased and FAP-related surgery should not be delayed.

Following the review of the submitted documentation, the responses provided at the oral hearing and the proposed SPC and letter of undertaking, the CPMP agreed that further long-term data was needed to support the efficacy and safety of the product.

In the pivotal trial submitted in support of the marketing authorisation application for Onsena, celecoxib 400 mg BID was shown to induce a reduction in polyp number; colorectal polyp number was decreased by 28.05 from baseline, a change that was statistically significant ($p=0.003$) when compared to the change in polyp number in patients receiving placebo. However, the clinical relevance of such a decrease in polyp number was unclear. Therefore the CPMP asked the applicant, to provide a preliminary protocol of a prospective confirmatory controlled trial with reference to the efficacy and safety of Onsena with clinically “hard” endpoints. The applicant should also show that such a protocol is feasible.

In response to the CPMP request, the applicant proposed to conduct an observational, historically controlled FAP registry study designed to gather data on the long-term use and safety of Onsena in current clinical practice and to assess the impact of its use on endoscopic surveillance and FAP-related outcomes.

A number of issues were identified with reference to the proposed study that needed further discussion at a CPMP ad hoc Expert meeting:

- 1/ In the view of the experts, would the applicant’s proposed protocol of a historically controlled registry study be adequate to provide useful information regarding the clinical relevance of the demonstrated reduction in polyp number?

In particular, would it be possible, through this study, to evaluate ‘hard’ **efficacy** endpoints such as:

- Prolongation of the time to FAP-related surgical events;
- Prolongation of the time to FAP-related adverse events, defined as time to the first of any of FAP-related cancers, desmoid tumors requiring procedural intervention, symptoms related to FAP that require hospitalisation/ procedural intervention, or death related to FAP.

Furthermore, would the proposed study be adequate to optimise the collection of long-term **safety** data?

The conclusions of the Experts were:

No, the proposed registry study would not gather useful efficacy results for the following reasons:

- Open design without randomisation.
- Problems associated with the use of historical controls.
- Definition of endpoints.
- Room for introduction of biases due to the proposed study design.
- Influence of rectal bleeding on performance of polypectomy.
- Relevance of population to be studied.
- Lack of power to detect statistically significant differences between recruited patients and historical controls.

As a result the proposed study would yield uninterpretable efficacy results.

However, in terms of safety the group agreed that the proposed study could provide some useful information provided that a number of improvements were made to the protocol.

- 2/ If the answer to any aspect of the first question is no, would an alternative study design be more appropriate?

The conclusions of the Experts were:

The group did not identify any plausible alternative design for a feasible study that would address the concerns of the CPMP, apart from a classical randomised controlled clinical trial design with a very long duration. Only such a study design would generate interpretable results. Ideally, such a study should be applied within the subset of the population that has already gone through colon resection with sufficient statistical power to detect the endpoints chosen. However, such a study would be impossible within acceptable timeframes. Furthermore, it was acknowledged that the wide off-label use of celecoxib might also further affect the feasibility of a randomised controlled clinical trial.

The Applicant addressed issues previously defined by the CPMP related to the feasibility of the proposed protocol and the potential efficacy and safety data that the study might generate at an oral hearing during the CPMP ad hoc expert meeting and at an oral hearing before the CPMP.

Following the review of all the submitted documentation, the responses provided at the oral hearings and the final SPC and final letter of undertaking, the CPMP agreed there is an unmet medical need for additional therapeutic tools in the management of patients with FAP. The committee considered that Onsenal has shown efficacy that is encouraging and may be clinically relevant and that allows a conclusion on an acceptable benefit/risk despite the limited efficacy and safety data available.

The CPMP concluded that a marketing authorisation for Onsenal will be granted under exceptional circumstances, subject to fulfilling the quality follow-up measure and clinical specific obligation undertaken by the Applicant. The indication for which the medicinal product in question is intended is encountered so rarely that the Applicant cannot reasonably be expected to provide comprehensive data on the safety and efficacy of the medicinal product. In order to collect additional data, the applicant has committed to complete a clinical study post-authorisation within pre-specified time frames, the results of which shall form the basis of an annual re-assessment of the benefit/risk profile:

Clinical aspects:

The Company commits to undertake a registry-based observational study to generate further efficacy and safety data. The study will be initiated within 1Q2004, with analysis of historical controls and registration of new patients receiving celecoxib in the study. In Europe the study will start once the product is available, post-registration.

Reports on recruitment and progress of the study will be provided on a biannual basis in line with submission of PSURs. The final study report will be submitted in 3 Q 2009.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Onsenal for *“the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance (See SPC section 4.4).*

The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated (See SPC sections 4.4 and 5.1)”, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

6. Post-marketing experience

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 celecoxib are as follows:

- Gastrointestinal toxicity

Available data indicated that significant and consistent gastrointestinal benefit of COX-2 inhibitors compared with conventional NSAIDs has not been demonstrated. The clinical data provided specifically for celecoxib were consistent with a GI benefit compared with naproxen. GI safety concerning complicated ulcers was similar to ibuprofen and diclofenac.

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 celecoxib require that 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 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.

It can be considered that there is a trend towards a higher MI risk associated with the use of celecoxib compared to naproxen and diclofenac. In contrast to COX-1 inhibiting NSAIDs, COX-2 inhibitors, including celecoxib, have no anti-platelet effects in therapeutic doses. 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 celecoxib, 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

When celecoxib was compared to NSAIDs, especially to diclofenac, the incidence of skin reactions, especially of rash, was significantly higher in MAA Trial, CLASS and SUCCESS. Results from clinical trials give reason for the conclusion that celecoxib-treated patients are at higher risk for developing rash than diclofenac-treated patients and possibly also at higher risk of developing urticaria than patients treated with other NSAIDs.

Spontaneous reports of hypersensitivity reactions (anaphylaxis/angioedema) were not very frequent for celecoxib. Because of the lack of relevant information no further statement on possible risk factors for the development of angioedema/anaphylaxis in celecoxib-treated patients can be met.

Furthermore, single cases of serious cutaneous adverse reactions, i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported for celecoxib. The absolute numbers and estimates for frequency suggest that these adverse reactions occur very rarely and frequency seems not to be different from conventional NSAIDs.

The statement in section 4.4 “Special warnings and special precautions for use” relating to hypersensitivity and serious skin reactions with Onsenal was already in line with these adopted conclusions resulting of 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 Onsenal:

- to promote the safe use of Onsenal 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.

Medicinal product no longer authorised