EMA/CHMP/444155/2011
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Joicela

lumiracoxib

**Procedure No.:** EMEA/H/C/002104/

Applicant: Novartis Europharm Limited

## Note

Rapporteur's day 180 assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

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LIST OF ABBREVIATIONS

| | |
|---|---|
| ABP | ambulatory blood pressure |
| ACE | angiotensin converting enzyme |
| ADBP | ambulatory diastolic blood pressure |
| ADME | absorption, distribution, metabolism, excretion |
| AE | Adverse Event |
| ALT | alanine aminotransferase / serum glutamic pyruvic transaminase (SGPT) |
| ANCOVA | analysis of covariance |
| APTC | Antiplatelet Trialists' Collaboration endpoint |
| ASBP | ambulatory systolic blood pressure |
| AST | aspartate aminotransferase / glutamic oxaloacetic transaminase (SGOT) |
| AUC | area under the concentration time curve |
| b.i.d./bid | *bis in die*/twice a day |
| BMI | body mass index |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| CCV | cardiovascular and cerebrovascular |
| CEL | celecoxib |
| CHF | congestive heart failure |
| CHMP | Committee for Medicinal Products for Human use |
| CI | confidence interval |
| $C_{max}$ | maximum (peak) drug concentration in plasma, during multiple dosing |
| COX189 | lumiracoxib |
| COX-1 or -2 | cyclo-oxygenase-1 or -2 |
| Cr | creatinine |
| CV | cardio- and cerebrovascular |
| CYP2C9 | cytochrome P450 isoform 2C9 |
| DBP | diastolic blood pressure |
| DILI | drug-induced liver injury |
| DPDA | difficulty performing daily activities |
| DSMB | drug safety monitoring board |
| DVT | deep vein thrombosis |
| EMEA | European Medicines Agency |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| Hct/hct | hematocrit |
| HR | hazard ratio |
| $H_2A$ | histone 2A |
| IBU/Ibup | ibuprofen |
| ID | initial dose |
| ITT | intent-to-treat |
| HLA | human leukocyte antigen |
| LLN | lower limit of normal |
| LOCF | last observation carried forward |
| L-RAP | lumiracoxib restricted access program |
| LSM | least squares mean |
| LUM | lumiracoxib |
| MASBP | mean ambulatory systolic blood pressure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | major histocompatability complex |
| MI | myocardial infarction |
| NAP | naproxen |
| NPV | negative predictive value |
| NSAID(s) | non-steroidal anti-inflammatory drug(s) |
| OA | osteoarthritis |
| OARSI | Osteoarthritis Research Society International |
| o.d./od/QD | *omnia in die*/once a day/every day |
| OMERACT | Outcome Measures in Arthritis Clinical Trials |
| OTC | over the counter |
| PASS | Post approval safety study |
| PD | pharmacodynamic |
| PE | pulmonary embolism |
| $PGE_2$ | prostaglandin $E_2$ |

| | |
|---|---|
| PgWP | Pharmacogenomics Working Party |
| PK | pharmacokinetic |
| POB | upper GI perforation, obstruction or bleeding |
| PPI | proton pump inhibitor |
| PPV | positive predictive value |
| PT/PTT | post-text/post-text table |
| PUB | upper GI perforation, obstruction, bleeding or symptomatic ulcer |
| RA | Rheumatoid arthritis |
| RCT | randomized controlled trial |
| RMP | Risk Management Plan |
| RR | relative risk |
| SAE | Serious Adverse Event |
| SBP | systolic blood pressure |
| SBS | Summary of Biopharmaceutic Studies and Associated Analytical Methods |
| SCARs | severe cutaneous adverse reactions |
| SCE | Summary of Clinical Efficacy |
| SCPS | Summary of Clinical Pharmacology Studies |
| SCS | Summary of Clinical Safety |
| SmPC | Summary of Product Characteristics |
| SNP | Single nucleotide polymorphism |
| SOC | system organ class |
| TARGET | Therapeutic Arthritis Research and Gastrointestinal Event Trial (0117-2332) |
| TARGET PG Substudy | Study 0117-2332ad1 |
| TIA | transient ischemic attack |
| t.i.d./tid | *ter in die* |
| $t_{max}$ | time to reach $C_{max}$ |
| $TxB_2$ | thromboxane $B_2$ |
| $T_{1/2}$ | terminal half time |
| ULN | upper limit of normal |
| UTE | unsatisfactory therapeutic effect |
| VAS | visual analog scale |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# EXECUTIVE SUMMARY

## *Problem statement*

This is an application for Joicela 100mg film-coated tablets (lumiracoxib) under Article 8(3) of Directive 2001/83/EC as amended, for the following indication:

**Symptomatic relief in the treatment of osteoarthritis of the knee and hip in patients who are non-carriers of the DQA1*0102 allele.**

This product was first authorised in the EU in 2003, as a national approval in the UK, and was subsequently approved in most of the EU by mutual recognition. European marketing authorisations were revoked in March 2008 following a Commission Decision resulting from concerns over hepatotoxicity.

The applicant has resubmitted clinical data from the original dossier, along with a limited amount of new data, most importantly the results of a retrospective pharmacogenetic study. The outcome of this study was the identification of a biomarker, the DQA1*0102 allele, which is claimed to identify patients at risk of lumiracoxib-related hepatotoxicity. Only non-carriers of the DQA1*0102 allele would be offered lumiracoxib. The indication is also limited to OA hip and knee, and the posology is 100mg daily. Other than the requirement to be a non-carrier for DQA1*0102, the indications and posology are identical to those agreed by member states during the mutual recognition procedure. The applicant also proposes post-approval safety measures, including a post-approval safety study and a restricted patient access program.

## *About the product*

Lumiracoxib is a fluorophenyl acetic acid derivative which acts as a selective COX-2 inhibitor. This class of drugs is widely used in the symptomatic treatment of osteoarthritis, and other rheumatological diseases. COX-2 inhibitors were developed to provide efficacy equivalent to non-steroidal anti-inflammatory drugs (NSAIDs) with a reduction in associated gastrointestinal complications.

The primary mechanism of action for all NSAIDs is attributed to inhibition of prostaglandin synthesis via the inhibition of cyclooxygenase (COX). Prostanoids derived from the cyclooxygenase pathway have both pathological and physiological roles. Prostaglandin E2 (PGE2), produced in pathological processes is a potent vasodilator that causes erythema and enhances oedema caused by other inflammatory agents such as bradykinin and histamine. PGE2 also plays a role in pain by sensitizing afferent nerve endings to the effects of bradykinin and histamine, and is also a potent pyretic agent. In the stomach, prostaglandins have a cytoprotective effect. Their function in the kidney is to modulate the effects of the nervous and endocrine control systems. Inhibition of prostaglandin production also accounts for NSAID common side effects, notably gastric ulceration, vascular constriction and renal impairment. With the discovery of an isoform of cyclooxygenase, cyclooxygenase-2 (COX-2), which is induced primarily in sites of inflammation, it has been hypothesized that a drug that selectively inhibits COX-2 isoenzyme would have the beneficial properties of NSAIDs without their associated side effects.

The product is presented as blister packs of 30 tablets, available in a 100 mg strength.

## *The development programme/Compliance with CHMP Guidance/Scientific Advice*

Lumiracoxib was nationally authorised as Prexige in the UK in 2003. In 2006, lumiracoxib was licensed via a mutual recognition procedure (UK/H/887-889/01-03/MR) in the following member states:

AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IC, IE, IT, LI, LU, LA, MT, NL, NO, PL, PT, SE, SL, SK.

A CMD(h) referral was made on the grounds of efficacy and safety. Consensus was reached following restriction of the indication to "Symptomatic treatment of osteoarthritis of knee and hip", with restriction of the dose to 100mg once daily. The indications of dysmenorrhoea, moderate dental pain after dental surgery and post orthopaedic surgery pain, and the strengths 200mg and 400mg were withdrawn.

Concerns over hepatotoxicity following assessment of post-marketing data resulted in an Article 107 referral in November 2007. In December 2007, CHMP recommended revocation of marketing authorisation in the EU, and a Commission Decision was published in March 2008. Lumiracoxib is still marketed in Mexico, Ecuador and The Bahamas under the trade name Prexige.

No formal CHMP scientific advice was given. However, informal advice was sought from EMEA Pharmacogenomics Working Party during a Voluntary Exploratory Data Submission briefing meeting in 2009, during which the Experts considered that retrospective data analysis from the TARGET study could support a submission of the DQA1*0102 biomarker without further prospective clinical studies.

In addition, national scientific advice was given during 2009 by DE, FR, SE and UK.

## *General comments on compliance with GMP, GLP, GCP*

CHMP have been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of Joicela 100mg film-coated tablets, including all batch release sites. CHMP have accepted copies of current manufacturer authorisations and GMP certificates issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The applicant confirms that all clinical trials conducted outside of the EU after April 2001 meets the ethical requirements of Directive 2001/20/EC. All clinical trials conducted outside the EU prior to April 2001 met equivalent ethical requirements through the Declaration of Helsinki, and also in some instances the ICH Tripartite Guidelines for GCP 1996 Directive 91/507/EEC, or in the US 21 CFR parts 50 and 56 concerning IC and IRB regulations, in addition.

## *Type of application and other comments on the submitted dossier*

This application is submitted in accordance with Article 8(3) of Directive 2001/83/EC (as amended) and is a full dossier with administrative, quality, non-clinical and clinical data. This centralised submission is under the optional scope of Article 3(2): 'significant innovation or interest of patients at community level' in view of the identification by the applicant of a genetic biomarker which is claimed to identify patients at increased risk of lumiracoxib-related hepatotoxicity, and thereby restore the risk-benefit ratio to an acceptable level.

Article 7 of the Paediatric Regulation applies to this application. A PIP is not required since a class waiver applies to this application for the treatment of primary osteoarthrosis (EMEA/180852/2009). Joicela is not intended for use in children and is contraindicated in children under 18 years of age.

# SCIENTIFIC OVERVIEW AND DISCUSSION

## *Quality aspects*

**Active substance**

The chemical-pharmaceutical documentation and Quality overall summary in relation to Joicela film-coated tablets are of sufficient quality in view of the present European regulatory requirements. Full information on the manufacture, control and stability of the active substance lumiracoxib is provided in the submitted dossier. The manufacturing process is adequately described and the provided information on the starting material adequate. The control tests and specifications for active substance product are adequately drawn up with satisfactory discussion in terms of the controls of genotoxic impurity. Stability studies have been performed with the active substance, see table below. Stress testing including a photostability study has been performed on the active substance. No significant changes in any parameters were observed. The proposed retest period of 60 months is justified.

**Finished Product**

The development of the product has been described, the choice of excipients is justified and their functions explained. The finished product manufacturing process and in-process controls have been adequately described. Information on manufacturing intermediate holding time has been provided with supporting bulk stability data. However, further information on the bulk container closure system should be provided.

Satisfactory control of the excipients has been described.

The product specifications cover the relevant parameters for this dosage form. However, the specifications for some impurities should be further tightened based on available stability data. Description of analytical procedures is considered to be adequate and validations data have been presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are generally in accordance to the ICH stability guideline. The control tests and specifications for finished product are adequately drawn up. The available stability data is presented below.

The available stability data is supportive of a proposed shelf-life of 36 months with no specific temperature storage conditions for Joicela 100mg film-coated tablets.

**Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

**Conclusions on the chemical, pharmaceutical and biological aspects**

With relation to the quality aspect, this application can be approved if all remaining concerns are satisfactory addressed.

## *Non clinical aspects*

## Pharmacodynamics

The selectivity and potency of lumiracoxib for COX-2 was investigated in *in vitro* enzyme, whole cell and whole blood assays, in comparison to celecoxib and/or rofecoxib and diclofenac. Lumiracoxib showed greater selectivity than other selective COX-2 inhibitors in the human whole blood assay.

The anti-inflammatory, analgesic and anti-pyretic activities of lumiracoxib were also investigated in a number of *in vivo* animal models. It was shown to have equivalent activities compared to other COX-2 selective inhibitors and the non-selective COX inhibitor diclofenac.

Metabolites of lumiracoxib were also studied in *in vitro* assays. In a human whole blood assay, the potency of lumiracoxib and its 4'-hydroxy metabolite were comparable, although in other assays this metabolite was 10 to 30 times less potent than lumiracoxib. The 4'-hydroxy metabolite was also studied in *in vivo* assays, and was found to have modest activity in the carrageenan-induced rat paw oedema assay.

In a rat tissue chamber model in which concentrations of compound in the chamber reportedly represent those in inflammed tissue, lumiracoxib entered the chamber faster that celecoxib and rofecoxib, and also was present at higher concentrations in the chamber 12 hours after dosing than in plasma. Therefore if this model reflects the situation in man, lumiracoxib may have a more rapid onset of action than the other COX-2 inhibitors tested.

Lumiracoxib exhibited less gastroenteropathic activity than diclofenac.

Renal effects were noted (reduced urinary PGE2 in water-loaded rats and water and electrolyte excretion in saline-loaded rats), which can be expected as COX-2 is expressed constitutively in the kidney. This indicates that kidney function should be monitored in patients.

There were indications of a slight CNS effect in behavioural studies in mice at doses of 10 mg/kg and higher, as well as a prolongation of phenobarbital-induced sleeping time in mice at similar doses, which may indicate a potential to interact with anaesthetics.

No significant activity of lumiracoxib was observed in cardiovascular, respiratory or gastric studies.

The estimated IC50 for hERG channel blockade was 51-fold the Cmax in man following a dose of 400 mg of lumiracoxib. Lumiracoxib decreased action potential parameters in sheep Purkinje fibres, suggesting it may have a potential to shorten QT interval. This occurred at a similar concentration to the Cmax in man. However, when plasma protein binding is taken into consideration, the free fraction in human plasma is about 50-fold less than the *in vitro* concentration at which action potential parameters were decreased. In telemetered monkeys, there were no notable effects on QT intervals at a dose of 500 mg/kg, at which the systemic exposure (3350 µg.h/ml) was over 100 times that in man following a therapeutic dose. Equally importantly, no effects on QT interval have been noted in the clinical trials.

## Pharmacokinetics

Orally administered lumiracoxib was extensively absorbed (90-100%) in all species, including man, with time to peak concentrations of lumiracoxib ranging from 0.5 to 4.0 hours. The elimination half-life of lumiracoxib ranged from 1 to 6.5 hours after an oral dose in the species studied, with the half-life of radioactivity in the plasma being longer (13 to 14 hours in mouse and rabbit, 45 hours in monkey, 56 hours in rat and 186 hours in man).

Lumiracoxib is highly protein bound (>0.98), predominantly to albumin in human serum.

The parent drug is the predominant circulating compound in all species following an oral dose. In each species, metabolism is similar after intravenous and oral dosing, and is qualitatively similar in all species.

Biotransformation occurs primarily by the hydroxylation (usually at the 4' position) of the dihaloaromatic ring, and/or oxidation at the 5-methyl position to produce 5-hydroxymethyl and then 5-carboxy metabolites. Subsequent glucuronidation or sulphation of the oxidative metabolites may then occur, or cyclisation to the corresponding lactams. Direct glucuronidation of lumiracoxib may also occur, particularly in the rat, although this does not appear to be a major pathway in man. Of the species tested, the monkey showed most similarity to man with respect to metabolite profile.

The major metabolites in human plasma are 4'-hydroxy-5-carboxy (M5), 5-carboxy (M11) and 4'-hydroxy (M23), the latter being pharmacologically active. The potency of 4'-hydroxy –lumiracoxib is 10 to 30 times less than that of lumiracoxib in an *in vitro* enzyme assay, but equipotent in the human whole blood assay. However, plasma exposure to this metabolite is only 15% of that of the parent, therefore it probably does not contribute greatly to the overall pharmacological effect.

In man, CYP2C9 is the main enzyme responsible for the metabolism of lumiracoxib. A general increase in the exposure to lumiracoxib glucuronide in volunteers treated with fluconazole (CYP2C9 inhibitor) suggests that this may be a compensatory pathway when CYP2C9 is inhibited.

The potential for genetic polymorphism to affect metabolism of lumiracoxib has been investigated *in vitro* and *in vivo* and reported in the clinical dossier. Reportedly, no evidence has been found to suggest that a group of poor metabolisers of lumiracoxib exists in the general population

Routes of excretion varied across the species. In rabbits, excretion was mainly renal whereas in monkeys, faecal excretion was the predominant route. Mouse, rat and man excreted a dose by renal and faecal routes, with a slightly higher proportion in the faeces in mouse and rat, and a slight preference for urinary excretion in man.

## Toxicology

The effects of lumiracoxib in acute toxicity studies in rats and mice included ataxia, reduced locomotor activity, impaired righting reflex and intestinal ulceration and/or perforation. Mortality and moribundity were associated with gastrointestinal toxicity.

Pivotal repeated-dose toxicity studies were conducted in rats (26-week oral study) and monkeys (39-week oral study). Dose range-finding studies were also conducted in rats, monkeys, mice and pregnant rabbits.

In mice administered lumiracoxib in feed for 2 or 13 weeks, target organs were the gastrointestinal tract and kidneys, with perforating gastrointestinal ulcers and renal tubular dilation observed in both studies.

Similar findings were noted in the 2- and 13-week dietary studies in rats, with perforating intestinal ulcers and their sequelae leading to death and moribundity, and tubular dilation again noted in the kidneys.

In 2-, 4- and 26-week oral rat studies in which the dose was given by gavage instead of in the diet, the kidney did not appear to be affected.

Lumiracoxib was relatively well-tolerated in the 4-week rat study, with only slight increases in spleen weight at the top dose of 50 mg/kg/day. In the 2- and 26-week studies, gastrointestinal toxicity was evident, with dose-dependent perforating gastrointestinal ulcers leading to mortality. As in the previous studies, there were additional pathological findings such as perforations and adhesions that were attributed to the gastrointestinal toxicity. Following a 4-week recovery period at the end of the 26-week study, no gastrointestinal lesions were noted. In the 26-week study, the NOEL was 3 mg/kg/day, due to the finding of some haematology changes in one animal at 10 mg/kg/day. The SPC section 5.3 states the systemic exposure multiple at the dose causing GI lesions.

The gastrointestinal tract and kidney were also identified as target organs in the monkey, although lumiracoxib was better tolerated in this species than in rodents. In a 4-week study, intestinal ulcers resulted in death (and the reduction of the high dose from 500 to 200 mg/kg/day). Secondary findings were similar to those found in rats. Gastrointestinal lesions were not seen in the 39-week study in monkeys in which the top dose was 150mg/kg/day. BUN was increased in the 2-, 4- and 39-week monkey studies. Renal tubular dilation and increased serum creatinine were noted only in the 4-week study at the high dose.

No treatment-related effects were noted after the 4-week recovery periods following the 4-week and 39-week studies. In the 39-week study, the NOEL was 10 mg/kg/day, due to the finding of increased BUN at 40 mg/kg/day. As the increase in BUN was minimal and did not correspond to changes in serum creatinine or renal pathology, the NOAEL was 40 mg/kg/day, At 150 mg/kg/day there were no GI lesions. However there were GI lesions at the top dose in the 4-week monkey study. The SPC section 5.3 again states the systemic exposure multiple at the dose causing GI lesions.

Findings of increased liver weights in the 39-week monkey study and in the 2-week i.v. study and 13-week dietary study in rats, were not associated with any clinical chemistry or histopathological evidence of hepatoxicity. Therefore the two main target organs for lumiracoxib are the gastrointestinal tract and the kidney. In view of the hepatotoxicity reported in humans, the applicant should re-examine the non-clinical toxicity data to investigate whether there are any signals for the liver toxicity observed clinically which could elucidate the mechanism of action.

Lumiracoxib was negative in an Ames test and in *in vivo* studies for clastogenicity. Positive results were noted in *in vitro* studies for chromosome aberrations, but only at concentrations that produced cytotoxicity. No structural alerts for genotoxicity were reported using two computer-based systems (DEREK and MCASE). Since there was evidence of clatogenicity only at cytotoxic concentrations, the results indicate that lumiracoxib can be considered to be non- genotoxic.

Carcinogenicity studies were carried out in mice and rats. Gastrointestinal toxicity was responsible for deaths, particularly at the higher doses. Survival in male mice was low at study termination, but survival in both studies was considered sufficient to enable assessment of the carcinogenic potential. No increases in the incidence of tumours were noted following treatment with lumiracoxib. At the highest doses in these studies, the systemic exposure (AUC) was 6.7 (mouse) and 12 (rat) times that in man following a dose of 1.43mg/kg/day.

In male rats, reproductive parameters were unaffected by lumiracoxib at doses up to 60□50 mg/kg/day. In females, decreases in numbers of corpora lutea, implantation sites and viable fetuses,

and increased preimplantation loss, occurred at ≥ 30 mg/kg/day. The SPC, section 4.4, contains the following warning:

"The use of Joicela, as with any medicinal product that inhibits COX-2, is not recommended in women attempting to conceive".

In embryo-fetal developmental studies, gastrointestinal toxicity was evident in the rat at ≥ 30 mg/kg/day, although embryo-fetal toxicity (decreases in implantation sites, number of viable fetuses and in fetal weights) was evident only at 100 mg/kg/day. At the NOEL for embryo-fetal toxicity (30 mg/kg/day), systemic exposure to lumiracoxib was 146558 ng.h/ml. There were no teratogenic effects in the rat.

In the rabbit, decreases in viable fetuses were associated with dose-related increases in resorptions at ≥ 60 mg/kg/day. Delayed ossification of sternebrae and phalanges were noted in fetuses at ≥ 60 mg/kg/day. Lumiracoxib did not appear to be teratogenic in the rabbit. At the NOEL for embryo-fetal development (20 mg/kg/day), systemic exposure was 37259 ng.h/ml. The mean concentration of lumiracoxib in pooled rabbit fetuses from the 200 mg/kg/day group was 21.8 ng/g tissue, which represents only 5% of the maternal plasma concentration (411 ng/ml) measured at the same time point.

In a pre- and post-natal development study in rats, gestation was prolonged slightly and the number of stillborn pups increased. Pup mortality increased on postpartum days 0-4. A NOEL was not established in this study. In keeping with other drugs of this class, the proposed SPC contraindicates lumiracoxib during the last trimester of pregnancy because of its potential to cause uterine inertia and premature closure of the ductus arteriosus.

Lumiracoxib did not produce immunotoxic effects in a 4-week study in rats, and a local lymph node assay in mice did not suggest a photoallergenic potential.

Proposed specifications for impurities in the DSS and FPS required that 534-00, a by-product of the synthesis (bromo-derivative), and degradation products 520-99 and 519-99, (an alcohol and aldehyde, respectively) should be qualified. A batch of lumiracoxib containing 1% 534-00 was negative in an Ames test and no more toxic in a repeated-dose toxicity study than lumiracoxib alone. A batch containing 2.2% of 519-99 and 5.1% 520-99 was negative in an Ames test and produced similar effects in an *in vitro* chromosome aberration test as the parent compound. This batch was potentially more toxic in a repeated-dose toxicity study than an unspiked batch, with increased mortality in male rats in the group receiving the spiked batch. A further repeated-dose study using a batch containing 1.9% of each of 519-99 and 520-99 showed similar toxicity to an unspiked batch of lumiracoxib and therefore these degradation products may be considered qualified at this level.

## Environmental risk assessment

The applicant conducted an environmental risk assessment. Lumiracoxib was not readily biodegradable and sorption to sludge has been found to be negligible. Therefore no terrestrial risk assessment has been deemed necessary for this API and the risk assessment consequently focused on the aquatic compartment and sediments.Based on the low octanol/water partition coefficients found for lumicracoxib at environmentally relevant pHs, no bioaccumulation is expected for this API and a PBT assessment was therefore not deemed necessary. Lumiracoxib shows moderate toxicity to the aquatic species used within the standard ERA test set, i.e. freshwater algae, Daphnia magna and fish early life-stages (fathead minnow). Moreover, no relevant inhibition of activated sludge respiration has been found for this API. The highest risk ratio for lumiracoxib in the Phase II-Tier A assessment has been

found for activated sludge in sewage treatment plants with PEC/PNECmicroorg accounting to 0.0014, indicating no concern for surface waters, sewage treatment plants and groundwater. Significant partitioning into sediments has been found for lumiracoxib with 18.4 % of the initially applied dose found in one of the sediments as parent substance at day 11, while in the other sediment 9 and 13.3 % of initially applied was found at day 11 and 25, respectively. One metabolite has been found at concentrations above 10% in the water and the applicant states that identification of this metabolite will be tackled. Based on this finding a study on the toxicity of lumiracoxib on sediment-dwelling larvae of Chironomus riparius has been initiated and the risk assessment will move on to a Tier B sediment assessment.

## Conclusion on non-clinical aspects

The non-clinical studies have demonstrated that lumiracoxib is a selective COX-2 inhibitor, targeting the gastrointestinal tract and kidney in toxicity studies. There are no major objections. There are no other concerns except for

(1) the request that the applicant re-examine the non-clinical toxicity data to attempt to elucidate the mechanism of liver toxicity reported in humans

(2) ERA (see below)

(1) In view of the hepatotoxicity reported in humans, the applicant should re-examine the non-clinical toxicity data to investigate whether there are any signals for the liver toxicity observed clinically which could elucidate the mechanism of action.

***CHMP comment:***

The Applicant has stated that re-examination of the non-clinical toxicity data has not been able to elucidate the mechanism of hepatotoxicity. The Applicant argues that the failure of non-clinical studies to predict idiosyncratic liver toxicity is well known and therefore attempts to study this effect non-clinically have proven unsuccessful. This is a reasonable argument.

This issue is considered to be resolved.

(2) Concerning the ERA.

The applicant should:

(i) identify the metabolite found at concentrations greater than 10% in the water phase

(ii) complete the ongoing study on *Chironomus riparius*

***CHMP comment:***

(i)The metabolite has been identified as 5-carboxy-lumiracoxib.
This issue is considered to be resolved.

(ii)The objective of the ongoing study in Chironomus riparius was to determine the impact of 14C lumiracoxib applied to sediment in a sediment-water exposure system. There was no significant reduction in emergence rate of midges exposed to all treatment levels when compared to controls. No risk to the sediment compartments is expected.

This issue is considered to be resolved.

### *Clinical aspects*

More than 40 clinical studies have been performed with lumiracoxib using different comparators, mostly ibuprofen, naproxen and celecoxib. In the indication OA, 18 trials have been conducted plus 3 extension studies. The clinical development program of lumiracoxib also comprised multiple trials in different indications (acute pain, primary dysmenorrhea, acute gout, rheumatoid arthritis) and at higher doses than 100mg daily.

## Pharmacokinetics

### Summary of clinical pharmacology studies in healthy volunteers:

| Study no: | Objective | Population | | Dose in mg (all oral and o.d. unless indicated) | N |
|---|---|---|---|---|---|
| [Study 0101] | SD, Safety/tolerability, PK/PD | HY | M | 25, 50, 100, 200, 400, 800 | 48 |
| [Study 0102] | MD, Safety/tolerability, PK/PD | HY | M | 50, 100, 200, 400, 300 b.i.d. | 40 |
| [Study 0106] | SD, ADME, 14C-COX189 | HY | M | 400 | 4 |
| [Study 0107] | MD, Safety/tolerability, PK/PD | HY | M | 200 b.i.d. | 65 |
| [Study 0121] | SD, Tab. bioav., food effect | HY | M | 200 | 20 |
| [Study 0123] | SD, Regional absorption | HY | M | 100 | 11 |
| [Study 0134] | MD, DDI/warfarin | HY | M/F | 400 | 24 |
| [Study 0135] | SD, DDI/omeprazole/antacid | HY | M/F | 400 | 14 |
| [Study 0136] | SD, Renal impairment | HY/RI | M/F | 200 | 16 |
| [Study 0137] | SD, Hepatic impairment | HY/HI | M/F | 400 | 16 |
| [Study 1101] | SD, Saf & tol, PK/PD, Japan | HY | M | 25, 50, 100, 200, 400, 800 | 48 |
| [Study 1102] | SD, Food effect, Jap. | HY | M | 200 | 12 |
| [Study 1103] | MD, Safety/tolerability, PK, Jap. | HY | M | 200, 400, 200 b.i.d. | 24 |
| [Study 2311] | MD, GI safety, endoscopy | HY | M/F | 800 | 25 |
| [Study 2313] | SD, DDI, with fluconazole | HY | M/F | 400 | 13 |
| [Study 2314] | MD, Renal safety/PD | HY | M/F | 200, 400 | 56 |
| [Study 2315] | SD, Bioequivalence, food effect | HY | M/F | 400 | 20 |
| [Study 2326] | MD, DDI/oral contraceptive | HY | F | 400 | 53 |
| [Study 2330] | SD, Bioequivalence | HY | M/F | 400 | 48 |
| [Study 2331] | SD, Absolute oral bioavailability | HY | M/F | PO: 200 IV: 50 or 100 | 15 |
| [Study 2336] | SD, Dental pain, PK/PD | HY | M/F | 400 | 318 |
| [Study 2349] | MD, DDI/aspirin, PD | HY | M/F | 400 | 28 |
| [Study 2350] | SD, Renal impairment, mild/moderate, PK | HY/RI | M/F | 200 | 24 |
| [ Study C2101] | SD, bioequivalence suspension versus tablet | HY | M/F | 200 | 18 |
| [Study D2103] | SD, Tolerability, PK, oral K+ salt versus free acid, IV, IM | HY | M/F | IV: 80, 160, IM: 40, PO: 260 | 20 |

DDI = Drug-drug interaction, HI = Hepatic impaired patients, HY = Healthy subjects, M = Male, F = Female, RI = Renal impaired patients, PO= per os, IV=intravenous, IM= intra muscular, SD = Single dose, MD = Multiple dose, o.d. = once a day, b.i.d.= twice a day

### Summary of clinical pharmacology studies in patients:

| Study no: | Objective | Population | | Dose in mg (all oral and o.d. unless indicated) | N |
|---|---|---|---|---|---|
| [Study 0104] | PK in OA patients to 28 days | OA | M/F | 50, 100, 200 b.i.d., 400 mg o.d. | 52 |
| [Study 0105] | PK in RA patients to 28 days | RA | M/F | 50, 100, 200 b.i.d., 400 mg o.d. | 43 |
| [Study 0108] | DDI/methotrexate | RA | M/F | 400 | 18 |
| [Study 0111] | PK in OA patients to 91 days | RA | M/F | 200, 400 | 65 |
| [Study 0112] | PK in OA patients to 91 days | OA | M/F | 200, 400 | 62 |
| [Study 0122] | plasma vs synovial fluid PK | RA | M/F | 400 | 22 |
| [Study 2312] | PK in RA patients | RA | M/F | 800, 1200 | 25 |
| [Study 2316] | PK in OA patients | OA | M/F | 100 | 16 |
| [Study 0132] | SD, PK in knee/hip arthroplasty | OA | M/F | 400 | 12 |
| [Study 2320] | MD, PK/PD in OA patients | OA | M/F | 400, 800 | 49 |
| [Study 2475] | MD, PD/PK in OA patients | OA | M/F | 100 | 27 |

DDI = Drug-drug interaction, OA = Osteoarthritis patients, RA = Rheumatoid arthritis patients, M = Male, F = Female, SD = Single dose

**Pharmacokinetics**

The pharmacokinetic of lumiracoxib has been investigated in a total of 23 studies in healthy subjects and in 11 studies in patients. A total of 1333 subjects were included in the phase I studies (942 healthy subjects and 391 patients).

A population pharmacokinetic analysis was performed on data from two studies performed in patients with osteoarthritis or rheumatoid arthritis at doses of 50, 100, 200 mg b.i.d. or 400 mg q.d. for 28 days. A total of 91 subjects were included in the analysis. The demographic factors weight, age, gender and race were tested for influence on volume of distribution and clearance of lumiracoxib.

Pharmacokinetic parameters were in the majority of studies calculated by using non-compartmental methods. Standard statistical methods including ANOVA were applied. In an extended statistical analysis,

data from 16 studies were analysed to evaluate potential influence of gender, race, age and weight on the pharmacokinetics of lumiracoxib.

The analytical methods employed have been properly validated and quality control checked within the respective studies.

**Absorption**

The median Tmax observed in the studies are in accordance with the suggested SPC wording, i.e. Cmax is attained within approximately 2 hours (range 0.5-4 h approximately). An absolute bioavailability of approximately 74 % was observed.

After intake of high-fat food, no significant food effect was observed (19 % decreased Cmax with high fat food). The product information states that lumiracoxib may be taken with or without food.

Following repeated once daily dosing for four weeks with 100 mg (the recommended dose) in osteoarthritis patients, the mean (SD) values of Cmax and AUC0-24 were 3.3 µg/ml, and 11 µg x hr/ml, respectively.

A regional absorption study showed that the Cmax is increased if specifically absorbed from the small distal bowel compared to stomach, likely an effect of higher pH and therefore dissolution.

The final formulation was used in phase III studies, hence no extrapolation is made.

**Distribution**
The volume of distribution after intravenous administration is 567±107 L (Vdss). The protein binding is high, approximately 98-99%, with an almost exclusive binding to albumin. No concentration dependency was evident in a concentration range from 0.1-100 µg/ml.

**Elimination**
Lumiracoxib is metabolised quite extensively, although the first pass effect is limited. The applicant states that CYP2C9 is the major enzyme responsible, however the interaction studies with the CYP2C9 inhibitor fluconazole does not support this.

The majority of the dose is excreted as metabolites in urine and faeces, on average 51 % and 41 % respectively. The recovered amount of unchanged lumiracoxib was 3.3% and 2 % in urine and faeces respectively. The identified part of the dose was approximately 78 % in total (lumiracoxib and metabolites). The majority of the total radioactivity in plasma during the first hours after dose is unchanged drug, approximately 80-90 % during the first 2.5 hours, then 38 % up to 48 hours. The total radioactivity recovered was nearly complete (97%) by 168 hours.

*In vivo* metabolite profiling was performed up to 168 hours. The major metabolites in plasma are 4-hydroxy-, 5-carboxy- and 4-hydroxy-5 carboxy-lumiracoxib. Direct glucuronidation is a minor pathway, 2.6 % of the dose in the urine. Sulphated and glucuronated conjugates are also formed via phase II metabolism.

Clearance and terminal half-life determined from intravenous administration was approximately 7.7 L/h and 4 hours, respectively. The renal clearance was found to be limited, from 0.05-0.2 L/h. A single dose study in healthy volunteers demonstrated a plasma half-life of 3.4 hours for the 100mg dose.

The pharmacokinetics of lumiracoxib has been shown to be dose and time proportional for doses between 25-800 mg. Steady state is reached during the first day of treatment and no accumulation is expected upon once daily dosing.

Regarding the activity of metabolites, the 4´-hydroxy derivative demonstrated some activity, but was about 3-fold less potent and selective than lumiracoxib in the human whole blood assay, and 10- and 30-fold less potent in the COX-1 and COX-2 enzyme assays, respectively. The other metabolites did not show any activity. The plasma levels of the major metabolites after a 200 mg dose of lumiracoxib (from the results of healthy volunteers in the renal impairment study) were all lower or in the same range as exposure to lumiracoxib. The protein binding of the 4´-hydroxylumiracoxib was similar to lumiracoxib.

A study evaluating the influence of polymorphism in CYP2C9 has been performed. Approximately 10 % and 7 % have the *2 and *3 alleles, known to have a reduced substrate turnover for tolbutamide and warfarin. There is a highly limited dataset on individuals with *2/*2 and *2/*3 (2 and 1 subjects) and no subject with *3/*3. Since no subject with *3/*3 was included in this analysis, the results should be interpreted with caution. This is because there is quite a large difference in the catalytic efficiency between the CYP2C9*2 and CYP2C9*3 as seen from the Vmax/Km data provided by the applicant. Although CYP2C9 is not the only metabolising enzyme, there may be a potential predictive value of CYP2C9 allele and hepatotoxicity. Therefore, the applicant should comment if there are any data on the effect of 2C9*3/*3 on the risk for lumiracoxib-related hepatotoxicity, in DQA1*0102 carriers and DQA1*0102 non-carriers.

**Variability**

The intra-subject variability was modest, approximately 10 % for AUC and 20-30 % for Cmax. The inter-subject variability was approximately 30 % for both AUC and Cmax.

**Pharmacokinetics in target population**

The pharmacokinetics in target population at the recommended dose was evaluated. There are no signs of any large differences compared to healthy volunteers. Synovial fluid concentrations were estimated in a population pharmacokinetic model. The model was sparsely described. While reasonable predicitions of plasma concentrations are obtained, the synovial fluid concentration predictions appear to be upward biased. The applicant claims in the product information, section 5.2 that the concentrations of lumiracoxib are higher in the synovial fluid from 5 hours after dose and remain higher up to end of dosing interval (24 h). It is questionable if this is the case.

**Special populations**

The applicant has investigated the exposure increase in patients with mild, moderate and end stage renal impairment requiring dialysis. Lumiracoxib is suggested to be contraindicated in patients with moderate and severe renal impairment. No unbound clearances were measured, although the applicant stated that the protein binding was not changed. No significant changes in the levels of lumiracoxib were observed. An approximate 9-fold increase in the exposure of 4-OH, 5-COOH comparing healthy subjects with patients with endstage renal impairment was observed. The exposure increase in patients with mild and moderate renal impairment is approximately 2-fold of all major metabolites (4-hydroxy-, 5-carboxy-, and 4-hydroxy, 5-carboxylumiracoxib).The safety implications of the increases in concentrations of the metabolites are not known.

In patients with moderate hepatic impairment, no significant change in the pharmacokinetics of lumiracoxib was observed. The report stated that the estimated binding exceeded the level that could be accurately measured (>98 %), therefore a difference in exposure based on unbound concentrations between healthy and patients with hepatic impairment may have been missed. Since the reason for the earlier withdrawal of Prexige (lumiracoxib) was due to the observation of hepatic toxicity that could not be excluded to have been caused by lumiracoxib, hepatic impairment is a contraindication.

Out of the tested demographic factors in the extended statistical analysis from 16 studies (age, gender, race, body weight) body weight had the largest effect on clearance of lumiracoxib. It was found that a subject with a weight of 100 kg would have an exposure 0.78 that of a subject of 75 kg. This was also in rough accordance with the estimation of influence of weight from the population pharmacokinetic analysis. A twofold increase in weight was estimated to result in a 44 % increase of clearance. The influence of body weight does not seem to warrant any dose adjustments.

A minor effect of age was observed, however the number of subjects older than 75 was highly limited (n=8). The pharmacokinetics of subjects younger and older than 65 years was calculated and a 15 % increased exposure in subjects older than 65 years was found. Regarding race, Blacks/Afro Americans (n=19) had a 16 % higher AUC than Caucasians (n=392). Japanese subjects (n=30), had a 10 % higher AUC than Caucasians. Between men (n=249) and women (n=250), there was a 6 % higher AUC in women and 11 % higher Cmax. The influence of age, race and gender does not seem to warrant any dose adjustments. It should however be included in the product information that the number of subjects older than 75 years was highly limited.

No investigation of the pharmacokinetics in children has been made. This is in accordance with the waiver granted from PDCO.

**Interactions**

*In vitro*

CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 were evaluated in terms of being responsible for the metabolism of lumiracoxib. CYP2C9 was shown to catalyze the metabolism of lumiracoxib. The selective inhibitor, sulfaphenazole, inhibited the metabolism of lumiracoxib in incubations with human liver microsomes *in vitro*.

Lumiracoxib demonstrated a modest inhibition of reactions catalyzed by CYP2C19 and CYP3A4 with IC50 values of >50 µM in each case. A more pronounced inhibition of CYP2C9 was observed with the probe substrate diclofenac with a Ki value of 7 µM. Lumiracoxib appears to have a low potential for interactions with compounds cleared by cytochrome P450 except for CYP2C9 where there is a possibility of decreased clearance of concomitantly administered substrates of CYP2C9.

The metabolism of lumiracoxib by CYP2B6 has been studied *in vitro*. CYP2B6 did not catalyze lumiracoxib metabolism *in vitro* to any detectable amount. The applicant has not investigated the potential for lumiracoxib to inhibit CYP2B6, but has committed to perform this study and submit a report by the end of 2011 as a follow-up measure.

A limited effect on the plasma protein binding of lumiracoxib by other concomitantly administered substances was shown. Lumiracoxib did not appear to affect the bound fraction of concomitantly administered drugs.

No *in vitro* induction studies have been performed. However there is no evidence of time dependent pharmacokinetics of lumiracoxib from *in vivo* studies.

*In vivo*

The interaction potential has not been fully investigated since no major metabolising enzyme was found. A larger interaction effect would have been expected with fluconazole if CYP2C9 would have been the dominant enzyme. No significant effect on the lumiracoxib pharmacokinetics more than a minor delay in tmax was observed with omeprazole, likely due to a slower gastric emptying. The antacid increased Cmax of lumiracoxib somewhat, but not to a clinically relevant extent. There are no indications of an effect of lumiracoxib on the pharmacokinetics of a low dose oral contraceptive combination of levonorgestrel and ethyinylestradiol. No significant effect on the pharmacokinetics of methotrexate is observed. However, there is a large variability in the figures and caution should be advised using low-dose methotrexate with lumiracoxib. Although no large effect was observed in the pharmacokinetics of S-warfarin or R-warfarin, a change in prothrombin time of approximately 15 % was observed, it is warranted to monitor the anticoagulant activity.

From the study in post-orthopaedic surgery patients after a 400 mg dose of lumiracoxib and concomitant different morphine doses, morphine reduced the bioavailability by approximately 50 % on average. Information on this should be included in the product information.

## Pharmacodynamics

The applicant submitted a number of studies, characterising the primary pharmacodynamics of lumiracoxib in man. The tissues used for these studies were:

| | |
|---|---|
| Human whole blood assays for ex vivo studies: | Studies 0101, 1101, 0107, 2311, 2314 |
| *In vivo* measurements of excretion of TxB2 metabolite: | Study 2314 |
| *In vivo* measurements of platelet aggregation: | Studies 0102, 2312 |
| Gastric mucosal biopsies for ex vivo studies: | Study 2311 |

The parameters used for measurement of COX activity were as follows:

| | |
|---|---|
| COX-1 Activity: | Serum TxB2; TxB2 metabolite (6-keto-PGF1-$\alpha$) |
| COX-2 Activity: | LPS-induced PGE2 synthesis |

In study 0101 of ex-vivo inhibition of PGE2 and TxB2 following a single dose of lumiracoxib, near complete inhibition of COX-2 was observed after 4 hours with 100mg. In study 0107, ex vivo coagulation-induced TxB2 production was used to assess COX-1 inhibition by lumiracoxib 200mg bid, compared to naproxen and placebo. TxB2 production was similar for lumiracoxib and placebo, and statistically significantly reduced by naproxen compared to both lumiracoxib and placebo. Reduced effect on gastric and duodenal mucosa at day 8 were demonstrated for lumiracoxib compared to naproxen. Study 2311 was a 3-period crossover randomised, placebo-controlled study to evaluate the effect of lumiracoxib on gastric and intestinal mucosa. By day 9, there were numerically less erosions with lumiracoxib 800mg QD compared to placebo, and significantly less than with naproxen 500mg bid. In Studies 0102 and 2312, multiple dose studies of several regimens, lumiracoxib did not inhibit platelet aggregation.

## Conclusions on clinical pharmacology

In general, the submitted data are adequate to support this application. The Applicant has committed to perform an *in vitro* study of the potential for lumiracoxib to inhibit CYP2B6 as a follow-up measure.

Remaining issues can be addressed by amendments to the SmPC as follows:

- There is highly limited information on the pharmacokinetics in subjects older than 75 years of age (section 4.2).
- The applicant should add the data from the interaction observed with opioids (section 4.5)
- The population pharmacokinetic model overpredicted the concentrations in synovial fluid. This information should not be included (section 5.2)
- Please add that the major metabolic pathway has not been determined (section 5.2).
- Data from the study in patients with mild/moderate renal impairment should be included (section 5.2)

However, as outstanding issues regarding clinical safety and risk management have been raised, it is considered premature to recommend conditions for marketing authorisation. Therefore SPC comments are not provided at this stage.

## Clinical efficacy

### *Dose-response studies*

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Efficacy Variables |
|---|---|---|---|---|---|
| **0104** | Parallel group, efficacy/safety study in knee and hip OA versus placebo and diclofenac | 510 | 4 weeks | LUM 50 mg bid<br>LUM 100 mg bid<br>LUM 200 mg bid<br>LUM 400 mg od<br>Diclofenac 75 mg bid<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC pain |
| **A2316** | Parallel group, efficacy/safety study in knee and hip OA versus placebo | 200 | 4 weeks | LUM 100 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC pain |

VAS = visual analog scale
† Patient's and physician's global assessments of disease activity

The applicant has submitted 2 dose-response studies in support of the claimed dose of 100mg od.

Study 0104

This was a double blind, randomised, parallel group, placebo-controlled dose-finding study. 583 patients with OA knee were randomised to 28 days of treatment with lumiracoxib, diclofenacor placebo as shown in the table above. This study showed the lowest dose of 50mg bid to be effective, but failed to distinguish between the different regimens.

Study 2316

This was a double blind, randomised, parallel group, placebo-controlled dose-finding study. 244 patients with OA of the knee or the hip were treated with lumiracoxib 100mg od or placebo for 28 days. The primary efficacy endpoint was overall joint pain intensity (100mm VAS) over the previous 24 hours in the most affected joint after 4 weeks. Lumiracoxib 100mg daily was statistically significantly superior to placebo.

### *Main clinical studies*

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Primary Efficacy variables |
|---|---|---|---|---|---|
| **Knee OA (claimed dose of 100 mg od, 200 mg od ID is not claimed)** | | | | | |
| **2360** | Parallel group, efficacy/safety study versus placebo and celecoxib | 1464 | 13 weeks | LUM 100 mg od<br>LUM 200 mg od ID*<br>Celecoxib 200 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Patient's global assessment of disease activity (VAS)†<br>-WOMAC total |
| **2361** | Parallel group, efficacy/safety study versus placebo and celecoxib | 1464 | 13 weeks | LUM 100 mg od<br>LUM 200 mg od ID*<br>Celecoxib 200 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Patient's global assessment of disease activity (VAS)†<br>-WOMAC total |
| **Hip OA (claimed dose of 100 mg od)** | | | | | |
| **2367** | Parallel group, efficacy/safety study versus placebo and celecoxib | 1200 | 13 weeks | LUM 100 mg od<br>Celecoxib 200 mg od<br>Placebo | -WOMAC pain<br>-WOMAC DPDA/function<br>-Patient's global assessment of disease activity (VAS)† |

*LUM 200 mg od ID = 100 mg od for 11 weeks preceded by an initial dose (ID) of 200 mg od for 2 weeks
VAS = visual analog scale, DPDA = difficulty performing daily activities (WOMAC function subscale)
† Physician's global assessment of disease activity was a secondary efficacy variable

The applicant has submitted 3 pivotal phase III clinical trials in support of the claimed indication. Studies 2360 and 2361, in OA knee were assessed during the MR procedure, and were found to be sufficient for marketing authorization of 100mg daily for symptomatic relief in the treatment of osteoarthritis of the knee and hip. Study 2367 has been assessed for the first time during the current procedure.

Study 2367 OA hip

This was an international, multicentre, randomised, double-blind, double-dummy, parallel group, placebo-controlled study to investigate the efficacy and safety of lumiracoxib 100 mg once daily for a period of 13 weeks in patients with primary hip osteoarthritis using celecoxib 200 mg once daily as a positive control.

The study was conducted in North America and Europe and recruited male and female patients aged 40 or over, with hip OA according to ACR criteria, presenting with OA pain, of greatest intensity in the target joint and of least 40 mm on a 0-100mm VAS in the last 24 hours. Patients were randomised in a ratio of 1:1:1 to lumiracoxib 100mg od, celecoxib 200mg od or placebo.

The primary objective was to demonstrate that lumiracoxib 100mg once daily was superior to placebo after 13 weeks treatment with respect to three co-primary efficacy variables:

- the pain sub-scale of the WOMAC© 3.1LK questionnaire
- the difficulty performing daily activities (DPDA) sub-scale of the WOMAC© 3.1LK questionnaire
- patient's global assessment of disease activity on a 100 mm visual analog scale (VAS)

Comparison of lumiracoxib with celecoxib 200mg od was a secondary objective.

The primary analysis was carried out on the ITT population using last observation carried forward (LOCF) to replace missing values.

1262 patients were randomised, of which. 951 completed the study, with a higher proportion of patients discontinuing prematurely from the placebo group (31%) than from either the lumiracoxib or celecoxib groups (21% and 22% respectively). Overall the demographic, background and baseline disease characteristics are well-balanced between the treatment groups. The age and sex distribution of the study population, and baseline disease characteristics reflect the intended indication.

The following tables include the results of the primary analysis of the three co-primary endpoints. For all three variables lumiracoxib was shown to be statistically significantly superior to placebo at the primary endpoint (Week 13) and also at earlier timepoints (Weeks 4 and 8). Similarly celecoxib was statistically superior to placebo at all timepoints and no significant difference was seen between lumircoxib and celecoxib at any time for any primary variable. These results were confirmed by three pre-specified sensitivity analyses.

**WOMAC (pain sub-scale score) treatment comparisons after 4, 8 and 13 weeks treatment (ITT population, LOCF)**

| Treatment Group | N | Least Square Mean | Contrast | Estimated Difference | 95% CI of Difference | p-value[1] |
|---|---|---|---|---|---|---|
| **Visit 3/Week 4 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 7.76 | LUM - CEL | 0.05 | -0.40, 0.50 | 0.844 |
| | | | LUM - Placebo | -1.08 | -1.53, -0.63 | <0.001* |
| Celecoxib 200mg o.d. | 418 | 7.72 | CEL - Placebo | -1.13 | -1.58, -0.67 | <0.001* |
| Placebo | 416 | 8.84 | | | | |
| **Visit 4/Week 8 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 7.17 | LUM - CEL | 0.01 | -0.48, 0.51 | 0.954 |
| | | | LUM - Placebo | -1.33 | -1.83, -0.84 | <0.001* |
| Celecoxib 200mg o.d. | 418 | 7.16 | CEL - Placebo | -1.35 | -1.85, -0.85 | <0.001* |
| Placebo | 416 | 8.51 | | | | |
| **Visit 5/Week 13 (Primary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 7.17 | LUM - CEL | 0.08 | -0.44, 0.60 | 0.766 |
| | | | LUM - Placebo | -1.12 | -1.63, -0.60 | <0.001* |
| Celecoxib 200mg o.d. | 418 | 7.09 | CEL - Placebo | -1.20 | -1.72, -0.67 | <0.001* |
| Placebo | 416 | 8.28 | | | | |

LUM = lumiracoxib 100 mg o.d.; CEL = celecoxib 200 mg o.d.
[1] ANCOVA with center, treatment, and baseline WOMAC® (pain sub-scale score) value.
Contrasts tested at the 5% significance level. *p<0.05; p-values not adjusted for multiplicity.

**Patients's global assessment of disease activity (VAS mm) treatment comparisons after 4, 8 and 13 weeks treatment (ITT population, LOCF)**

| Treatment Group | N | Least Square Mean | Contrast | Estimated Difference | 95% CI of Difference | p-value[1] |
|---|---|---|---|---|---|---|
| **Visit 3/Week 4 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 427 | 40.51 | LUM - CEL | -1.27 | -4.31, 1.77 | 0.412 |
| | | | LUM - Placebo | -9.30 | -12.35, -6.26 | <0.001* |
| Celecoxib 200mg o.d. | 419 | 41.78 | CEL - Placebo | -8.03 | -11.10, -4.96 | <0.001* |
| Placebo | 416 | 49.81 | | | | |
| **Visit 4/Week 8 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 427 | 37.28 | LUM - CEL | -2.11 | -5.29, 1.08 | 0.195 |
| | | | LUM - Placebo | -11.34 | -14.53, -8.14 | <0.001* |
| Celecoxib 200mg o.d. | 419 | 39.39 | CEL - Placebo | -9.23 | -12.44, -6.01 | <0.001* |
| Placebo | 416 | 48.62 | | | | |
| **Visit 5/Week 13 (Primary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 427 | 37.63 | LUM - CEL | 0.15 | -3.10, 3.39 | 0.929 |
| | | | LUM - Placebo | -8.59 | -11.84, -5.33 | <0.001* |
| Celecoxib 200mg o.d. | 419 | 37.48 | CEL - Placebo | -8.73 | -12.01, -5.46 | <0.001* |
| Placebo | 416 | 46.22 | | | | |

LUM = lumiracoxib 100 mg o.d.; CEL = celecoxib 200 mg o.d.
[1] ANCOVA with center, treatment, and baseline Patient's global assessment of disease activity value
Contrasts tested at the two-sided 5% significance level. *p<0.05; p-values not adjusted for multiplicity.

**WOMAC (Function/DPDA sub-scale score) treatment comparisons after 4, 8 and 13 weeks treatment (ITT population, LOCF)**

| Treatment Group | N | Least Square Mean | Contrast | Estimated Difference | 95% CI of Difference | p-value[1] |
|---|---|---|---|---|---|---|
| **Visit 3/Week 4 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 27.74 | LUM - CEL | 0.08 | -1.40, 1.55 | 0.917 |
| | | | LUM - Placebo | -3.77 | -5.25, -2.30 | <0.001* |
| Celecoxib 200mg o.d. | 417 | 27.67 | CEL - Placebo | -3.85 | -5.33, -2.37 | <0.001* |
| Placebo | 416 | 31.52 | | | | |
| **Visit 4/Week 8 (Secondary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 25.70 | LUM - CEL | -0.32 | -1.93, 1.29 | 0.695 |
| | | | LUM - Placebo | -5.09 | -6.70, -3.48 | <0.001* |
| Celecoxib 200mg o.d. | 417 | 26.02 | CEL - Placebo | -4.77 | -6.39, -3.15 | <0.001* |
| Placebo | 416 | 30.79 | | | | |
| **Visit 5/Week 13 (Primary analysis)** | | | | | | |
| Lumiracoxib 100mg o.d. | 424 | 26.08 | LUM - CEL | 0.34 | -1.33, 2.01 | 0.690 |
| | | | LUM - Placebo | -3.58 | -5.24, -1.91 | <0.001* |
| Celecoxib 200mg o.d. | 417 | 25.74 | CEL - Placebo | -3.92 | -5.59, -2.24 | <0.001* |
| Placebo | 416 | 29.65 | | | | |

LUM = lumiracoxib 100 mg o.d.; CEL = celecoxib 200 mg o.d.
[1] ANCOVA with center, treatment, and baseline WOMAC© (function/DPDA sub-scale score) value.
Contrasts tested at the two-sided 5% significance level. *p<0.05; p-values not adjusted for multiplicity.

For each of the three primary efficacy variables, lumiracoxib 100 mg o.d. was significantly superior to placebo after 13 weeks of treatment. There was no significant difference between lumiracoxib 100 mg o.d. and celecoxib 200 mg o.d. for the three primary efficacy variables. Analysis in the per-protocol population (LOCF) confirmed these results. Lumiracoxib was also statistically superior to placebo after 4 and 8 weeks of treatment for WOMAC© pain sub-scale score, WOMAC© DPDA sub-scale score, and

patient's global assessment of disease activity. No significant differences were seen between lumiracoxib 100mg o.d. and celecoxib 200 mg o.d. for these variables at Weeks 4 and 8.

Secondary efficacy endpoints were:

- WOMAC© 3.1 LK sub-scale scores (pain, DPDA, and stiffness) and total score by visit – for patient's functional status during the prior 48 hours
- Patient's global assessment of disease activity using a 0-100 mm VAS by visit.
- Physician's global assessment of disease activity using a 0-100 mm VAS by visit.
- Patient's overall pain intensity in the target hip using a 0-100 mm VAS by visit.
- Response to treatment according to OARSI criteria by visit.
- Number of acetaminophen/paracetamol rescue tablets taken since the previous visit

Patients also carried out pain assessments at home, each evening (approximately 12 hours after ingestion of study drug), by rating pain intensity in the target joint on a 100mm VAS, for 1 week after each clinic visit.

For all the secondary outcomes, lumiracoxib was shown to be statistically significant to placebo, and comparable to celecoxib.

Studies 2360 and 2361 knee OA

Both studies were of identical design and were 13-week, multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled, parallel groups trials of 2 different dose regimens of lumiracoxib (100 mg once daily for 13 weeks and 200 mg once daily initial dose for two weeks followed by 100 mg once daily for 11 weeks) in patients with primary knee osteoarthritis, using celecoxib (200 mg once daily) as a control.

Patients with symptomatic primary knee osteoarthritis (pain $\geq$ 40mm VAS at target joint) were randomised 1:1:1:1 to lumiracoxib 100mg once daily, lumiracoxib 200mg once daily for 2 weeks followed by 100mg once daily, celecoxib 200mg daily or placebo. In study 2360, 1551 patients were randomized, compared to 1684 in study 2361.

Joint primary efficacy endpoints :

- Overall OA pain intensity in the target knee (0-100mm VAS) after 13 weeks of treatment
- Patient's global assessment of disease activity (0-100 mm VAS) after 13 weeks of treatment
- Patient's functional status (using the WOMAC total score) after 13 weeks of treatment.

Efficacy results of individual treatments on the primary endpoints at 13 weeks, ITT population (LOCF) are presented in the tables below:

**Study 2360: Primary efficacy outcomes**

| | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | Lum 100 | 66.4 | 40.84 | **-6.69** | **-10.09 , -3.30** | **<0.001** |
| | Lum 200 / 100 | 65.4 | 39.42 | -8.11 | -11.52 , -4.71 | <0.001 |
| | Celecoxib | 66.4 | 41.83 | -5.70 | - 9.09 , -2.32 | <0.001 |
| | Placebo | 66.2 | 47.54 | | | |
| Patient assessment of disease activity (VAS mm) | Lum 100 | 63.1 | 39.62 | **-9.10** | **-12.41 , -5.80** | **<0.001** |
| | Lum 200 / 100 | 63.8 | 38.63 | -10.10 | -13.42 , -6.77 | <0.001 |
| | Celecoxib | 61.7 | 42.06 | -6.66 | - 9.96 , -3.36 | <0.001 |
| | Placebo | 62.5 | 48.72 | | | |
| WOMAC score | Lum 100 | 52.86 | 35.62 | **-7.42** | **- 9.75 , -5.09** | **<0.001** |
| | Lum 200 / 100 | 52.86 | 35.30 | -7.75 | -10.09 , -5.41 | <0.001 |
| | Celecoxib | 52.59 | 36.70 | -6.35 | - 8.67 , -4.02 | <0.001 |
| | Placebo | 53.13 | 43.05 | | | |

**Study 2361: Primary efficacy outcomes**

| | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | Lum 100 | 64.1 | 37.05 | **-5.09** | **(-8.04, -2.15)** | **<0.001** |
| | Lum 200 / 100 | 64.4 | 37.81 | -4.33 | (-7.28, -1.39) | 0.004 |
| | Celecoxib | 64.8 | 37.52 | -4.63 | (-7.57, -1.68) | 0.002 |
| | Placebo | 63.8 | 42.14 | | | |
| Patient assessment of disease activity (VAS mm) | Lum 100 | 63.1 | 37.72 | **-5.93** | **(-8.87, -2.99)** | **<0.001** |
| | Lum 200 / 100 | 61.6 | 39.99 | -3.66 | (-6.60, -0.71) | 0.015 |
| | Celecoxib | 62.9 | 39.77 | -3.88 | (-6.82, -0.94) | 0.010 |
| | Placebo | 62.9 | 43.65 | | | |
| WOMAC score | Lum 100 | 49.2 | 34.27 | **-3.92** | **(-5.98, -1.86)** | **<0.001** |
| | Lum 200 / 100 | 49.7 | 34.86 | -3.33 | (-5.40, -1.27) | 0.002 |
| | Celecoxib | 50.5 | 35.24 | -2.95 | (-5.01, -0.89) | 0.005 |
| | Placebo | 49.7 | 38.19 | | | |

Lumiracoxib 100mg, lumiracoxib 200mg od initial dose (ID), and celecoxib 200mg od were statistically superior to placebo and comparable to celecoxibfor treatment of OA of the knee with respect to:

- Overall OA (VAS) pain intensity in the target joint, after 2, 4, 8, and 13 weeks of treatment,
- patient's and physician's assessment of disease activity after 2, 4, 8, and 13 weeks of treatment
- WOMAC total and WOMAC stiffness, pain and DPDA scores, after 2, 8, and 13 weeks of treatment

Extension studies

Study 2361E was a 39-week, double-blind, active-controlled extension study to 2361. Patients who were exposed to placebo and completed the core study were randomised to lumiracoxib 100mg od or celecoxib 200mg od. After 26 weeks, there was no significant difference between lumiracoxib and celecoxib with respect to the 3 co-primary variables used in the core study. Study 2360E1 was an open label extension to 2360, in which patients completing the core study on celecoxib or placebo were switched to lumiracoxib 100mg od. The efficacy results provided some evidence of long-term maintenance of efficacy.

Supportive studies

The applicant has also submitted data from other clinical studies, as summarized in the following tables. Many are at higher doses of lumiracoxib, for non-claimed indications, and some are un-controlled. However, these studies are considered supportive for the efficacy of lumiracoxib 100mg once daily for the claimed indication.

Summary of supportive controlled efficacy trials in OA (claimed dose, OA of various joints):

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Efficacy variables |
|---|---|---|---|---|---|
| **OA of various joints (claimed dose of 100 mg od, 100 mg bid is not claimed):** | | | | | |
| **2369** | Parallel group, retention on treatment, safety/ efficacy study in knee, hip, hand, spine OA versus celecoxib | 3000 | 52 weeks | LUM 100 mg od<br>LUM 100 mg bid<br>Celecoxib 200 mg od | -OA pain intensity (Likert)<br>-Global assessments of disease activity (Likert)† |
| **2428** | Parallel group, safety/ efficacy study in knee, hip, hand, spine OA versus ibuprofen | 600 – 1650 ‡ | 4 weeks | LUM 100 mg od<br>Ibuprofen 600 mg tid | -OA pain intensity (Likert)<br>-Global assessments of disease activity (Likert)† |

† Patient's and physician's global assessments of disease activity
‡ upper limit of planned population was determined in a protocol-specified blinded interim data review of 600 completers, 1650 was the upper predefined cap.

Summary of other controlled efficacy trials in OA (higher doses, OA of various joints):

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Efficacy variables |
|---|---|---|---|---|---|
| **Knee OA (higher doses not claimed for OA):** | | | | | |
| **0109** | Parallel group efficacy / safety study in knee OA versus placebo and celecoxib | 1512 | 13 weeks | LUM 200 mg od<br>LUM 400 mg od<br>Celecoxib 200 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC pain<br>-WOMAC total |
| **0112** | Parallel group efficacy / safety study in knee OA versus placebo and celecoxib | 1512 | 13 weeks | LUM 200 mg od<br>LUM 400 mg od<br>Celecoxib 200 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC pain<br>-WOMAC total |
| **2364** | Parallel group efficacy / safety study in knee OA versus celecoxib in Asian patients | 700 | 6 weeks | LUM 200 mg od<br>Celecoxib 200 mg od | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)† |
| **Hip OA (higher doses not claimed for OA):** | | | | | |
| **0128** | Parallel group efficacy / safety study in hip OA versus placebo and rofecoxib | 495 | 13 weeks | LUM 400 mg od<br>Rofecoxib 25 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC pain<br>-WOMAC total |
| **Hand OA (higher doses not claimed for OA):** | | | | | |
| **2319** | Parallel group, efficacy / safety study in hand OA versus placebo | 498 | 4 weeks | LUM 200 mg od<br>LUM 400 mg od<br>Placebo | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-AUSCAN index |
| **OA of various joints (higher doses not claimed for OA):** | | | | | |
| **2307** | Parallel group safety / efficacy study in knee, hip, hand, spine OA versus rofecoxib | 304 | 6 weeks | LUM 400 mg od<br>Rofecoxib 25 mg od | -OA pain intensity (Likert)<br>-Global assessments of disease activity (Likert)† |
| **0126** | Parallel group, safety / efficacy study in knee, hip, hand, spine OA versus ibuprofen and celecoxib | 792 | 13 weeks | LUM 200 mg od<br>LUM 400 mg od<br>Celecoxib 200 mg od<br>Ibuprofen 800 mg tid | -OA pain intensity (Likert)<br>-Global assessments of disease activity (Likert)† |
| **TARGET (0117-2332)** | Parallel group, safety / efficacy study in knee, hip, hand, spine OA vs naproxen & ibuprofen | 18000 | 52 weeks | LUM 400 mg od<br>Naproxen 500 mg bid<br>Ibuprofen 800 mg tid | -OA pain intensity (Likert)<br>-Global assessments of disease activity (Likert)† |
| **Knee OA (higher doses not claimed for OA, short mechanistic studies)** | | | | | |
| **2301** | Parallel group, efficacy / safety study in knee OA vs placebo & celecoxib | 330 | 1 week | LUM 400 mg od<br>Celecoxib 200 mg bid<br>Placebo | Overall pain intensity difference (over 3-5 hrs, Day 0) |
| **2303** | Parallel group, efficacy / safety study in knee OA vs placebo & celecoxib | 400 | 1 week | LUM 200 mg od<br>LUM 400 mg od<br>Celecoxib 200 mg bid<br>Placebo | Overall pain intensity difference (over 3-5 hrs, Day 0) |

VAS = visual analog scale † Patient's and physician's global assessments of disease activity

Summary of uncontrolled trials:

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Efficacy variables |
|---|---|---|---|---|---|
| 2360E1* | Open-label extension study in knee OA | 1464 | 52 weeks | LUM 100 mg od | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)†<br>-WOMAC total |
| 2365 | Open-label study in knee OA or RA in patients in India | 135 (enrolled: 116 OA, 20 RA) | 6 weeks | LUM 200 mg od | -OA pain intensity (VAS)<br>-Global assessments of disease activity (VAS)† |

* Placebo and celecoxib patients completing 13 weeks of treatment in double-blind core Study 2360 were switched to lumiracoxib 100 mg od in the 39 week open-label extension Study 2360E1. Lumiracoxib patients continued on the same treatment.
VAS = visual analog scale, † Patient's and physician's global assessments of disease activity

Efficacy in DQA1*0102 non-carriers (intended population)

As the intended OA treatment population to receive lumiracoxib treatment are the DQA1*0102 non-carriers (approximately 65-70% of the overall population), the applicant has performed an analysis in the TARGET genetic sub-study, to evaluate whether efficacy in the DQA1*0102 non-carrier population is similar to that observed in the DQA1*0102-carrier population. Efficacy in carriers and non-carriers was compared using a 5-point Likert pain scale, a validated OA efficacy measure in TARGET.

**Table 4-16 Comparison of efficacy between DQA1*0102 carriers and non-carriers in lumiracoxib-treated patients (TARGET)**

| Efficacy endpoint | DQA1*0102 carriers (n=1518) | DQA1*non-carriers (n=3000) |
|---|---|---|
| | n (%) | n (%) |
| **Patient's pain assessment** | | |
| Improved | 945 (62.3%) | 1937 (64.6%) |
| Unchanged | 439 (28.9%) | 819 (27.3%) |
| Worsened | 121 (8.0%) | 203 (6.8%) |
| **Patient's global disease assessment** | | |
| Improved | 909 (59.9%) | 1910 (63.7%) |
| Unchanged | 425 (28.0%) | 742 (24.7%) |
| Worsened | 172 (11.3%) | 307 (10.2%) |
| **Physician's global disease assessment** | | |
| Improved | 902 (59.4%) | 1902 (63.4%) |
| Unchanged | 460 (30.3%) | 810 (27.0%) |
| Worsened | 140 (9.2%) | 245 (8.2%) |

A comparison of efficacy between DQA1*0102 carriers and non-carriers in lumiracoxib-treated patients showed a slightly increased efficacy in non-carriers for patient global disease assessment (p=0.029) and physician global disease assessment (p=0.036).

## Discussion on clinical efficacy

The claimed indication of symptomatic relief in the treatment of osteoarthritis of the knee and hip and the proposed posology of 100mg once daily are the same as those agreed following CMD(h) referral during the MR procedure UK/H/887-9/01-03/MR, apart from the requirement to be a non-carrier of

DQA1*0102. A marketing authorisation was granted in 26 member states based on the 2 pivotal OA knee studies 2361 and 2360. In the current submission, the applicant has included new clinical data from a pivotal OA hip study 2367.

Study 2367 is considered well-designed and to have been well-conducted, in accordance with the new CHMP OA guideline (*The Guideline on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis* CPMP/EWP/784/97 Rev.1). Studies 2360 and 2361 were also conducted in line with current guidelines. For each of the primary efficacy variables, lumiracoxib 100 mg o.d. was consistently and statistically significantly superior to placebo after 13 weeks of treatment. There was no significant difference between lumiracoxib 100 mg o.d. and celecoxib 200 mg o.d. The results of the primary analysis were shown to be robust in terms of the handling of missing data. The effect sizes observed in the pivotal hip study (2367), are relatively small, but are in line with those seen in the pivotal OA knee studies (2360 and 2361).

For the claimed dose and indications, the applicant has not provided comparative data with traditional NSAIDs such as ibuprofen, naproxen or diclofenac. However, celecoxib, another COX-2 inhibitor, is widely marketed and considered an appropriate choice of active control. None of the pivotal studies were powered to show non-inferiority to celecoxib, but the treatment effects were comparable, which is supportive of clinical significance of the observed effect sizes. Demonstration of non-inferiority is not required by the new CHMP OA guideline.

The patient population in the pivotal trials had primary osteoarthritis. Secondary OA was a specific exclusion. According to the *Guideline on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis* CPMP/EWP/784/97 Rev.1, it is acceptable to register product for 'treatment of osteoarthritis of the knee and the hip' if efficacy at the knee or hip level is demonstrated. No recommendation is made concerning the inclusion of patients with secondary arthritis. However it is considered acceptable to exclude patients with secondary arthritis on the grounds of homogeneity. Based on the pathophysiology of secondary arthritis, it is likely that lumiracoxib would demonstrate comparable efficacy to that observed in primary arthritis.

One year extension studies of the pivotal hip studies (2360 and 2361) provide some evidence of long-term maintenance of efficacy. Data from other trials, conducted at higher doses and/or different indications is considered supportive of efficacy at the claimed dose and indication.

The applicant has retrospectively analysed the available efficacy data from TARGET DQA1*0102 carriers and non-carriers treated with lumiracoxib, in support of the indication. The instrument is limited compared to those required for pivotal OA efficacy trials, as TARGET was primarily a safety study. However, the data suggests that efficacy is comparable. There appears to be a slight increase in efficacy in non-carriers.

## Conclusions on clinical efficacy

The results of the pivotal efficacy trials are considered robust. The efficacy data submitted is sufficient to support the claimed dose and indication.

## Clinical safety

Lumiracoxib was referred under Article 107 (EMEA/H/A-107/945) after the UK recommended suspension of marketing authorisation because of increasing concerns over hepatotoxicity from spontaneous reporting. The outcome was a CHMP opinion recommending revocation of marketing

authorisations in the EU. A Commission Decision was published in March 2008. The Article 107 assessments considered the available clinical trial database, including the more recent pivotal OA hip study (2367). No new clinical studies have been carried out since the Article 107 procedure. Lumiracoxib is still marketed in Mexico, Ecuador and, The Bahamas under the trade name Prexige. The applicant has provided copies of PSURs (plus bridging report and an addendum report) covering the period from 13 Sep 2003– 30 Sep 2009.

### Overview of CHMP safety referrals related to lumiracoxib:

| Type of Procedure | Procedure number | Procedure under Article | Date of Opinion |
|---|---|---|---|
| CHMP referral on COX-2 inhibitor | EMEA/H/A-31/632 | Art. 18 and 31 of Directive 2001/83/EC. | June 2005 |
| CHMP referral on NSAIDs | EMEA/H/A-5.3/800 | Art. 5(3) of Regulation (EC) No 726/2004 | November 2006 |
| CHMP referral on hepatic safety | EMEA/H/A-107/945 | Art. 107 of Directive 2001/83/EC | December 2007 |

This submission includes the results of a retrospective pharmacogenetic sub-study of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), a large controlled 52 week lumiracoxib safety study. The applicant has identified a biomarker, the DQA1*0102 allele, which is claimed to be effective in identifying patients at risk of lumiracoxib-related hepatotoxicity. Only non-carriers of the DQA1*0102 allele would be offered lumiracoxib. The applicant concludes that the risk of hepatotoxicity would be reduced enough to allow a positive risk-benefit to be concluded. To provide reassurance that the safety profile is maintained in the intended DQA1*0102 non-carrier population, the applicant has also performed a safety analysis in the lumiracoxib-treated patients who were genotyped from the TARGET study.

The applicant has submitted safety data from all completed short and long-term OA and RA studies, including TARGET, as shown below:

| Dataset | Population | Studies supplying patients |
|---|---|---|
| | **Main OA datasets** | |
| **D1** | Osteoarthritis short-term studies (up to 13 weeks exposure) | 0104, 0109, 0112, 0126, 0128, 2301, 2303, 2307, 2316*, 2319, 2360*, 2361*, 2364, 2365†,2367*, 2369*#, 2428* |
| **D2** | Osteoarthritis long term studies (1 year exposure, except TARGET) | 0112/0112E, 2360*/2360E*, 2361*/2361E*, 2369* |
| **TARGET** | Osteoarthritis (400 mg od for 1 year) | 0117 and 2332 |
| | **Datasets for analysis of special safety topics** | |
| **D3s** | Studies of 13 weeks duration + the first 13 weeks data from longer studies (0111, 2369, TARGET) | 0109, 0112, 0126, 0128, 2360*, 2361*, 2365†, 2367*, 2369*#, 0114, 0110, 0111#, 2335+ TARGET (0117 and 2332) |
| **D12r** | Double-blind OA studies of 1 year duration | 0112/0112E, 2361*/2361E*, 2369* + TARGET (0117 and 2332) |
| | **Large integrated datasets** | |
| **D9** | OA/RA short and long-term studies, except TARGET | 0104, 0105, 0109, 0110, 0111, 0112, 0112E, 0114, 0126, 0128, 2301, 2303, 2307, 2312, 2316*, 2319, 2335, 2335E, 2360*, 2360E*, 2361*, 2361E*, 2364, 2365†, 2367* and 2369* and 2428* |
| **D9+T** | Dataset 9+TARGET | |
| | **Datasets in non-claimed indications** | |
| **D7** | Rheumatoid arthritis | 0105, 0110, 0111, 0114, 2312, 2335/2335E1 |

* = studies including patients taking lumiracoxib 100 mg od, # 13 week data from a longer duration study
† Study 2365 included both OA patients (n=116, 85%) and RA patients (n=20, 15%)

### *Patient exposure*

More than 40 000 patients have received lumiracoxib in clinical trials. A total of 21,702 patients were exposed to lumiracoxib in the integrated dataset (Dataset 9 + TARGET). This equates to more than 11,850 patient years of exposure. This dataset includes all safety data from short and long-term OA and RA trials. For the claimed indication of OA at the claimed dose of 100mg once daily, there were 673.2 patient years of exposure in trials up to 13 weeks duration, and 1862.1 patient years of exposure in trials of 12 months.

**Table 1-9 Duration of exposure in OA and RA (Datasets 1, 2, TARGET and 9) by treatment**

| Duration (days) | COX189 100mg od | COX189 100mg bid | COX189 200mg od | COX189 400mg od | COX189 800mg od | Celecoxib 200mg od | Celecoxib 200mg bid | Rofecoxib 25mg od | Naproxen 500mg bid | Ibuprofen 800mg tid | Placebo |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Main OA datasets** | | | | | | | | | | | |
| **Dataset 1 (OA trials up to 13 wks)** | n=3314 | n=1615 | n=2011 | n=2108 | - | n=3524 | n=246 | n=257 | - | n=260 | n=2493 |
| Mean | 74.2 | 78.6 | 62.6 | 62.6 | - | 77.0 | 8.3 | 56.9 | - | 78.1 | 62.6 |
| SD | 29.38 | 26.49 | 31.51 | 34.28 | - | 26.69 | 1.33 | 25.17 | - | 26.08 | 35.08 |
| Median | 91.0 | 92.0 | 82.0 | 87.0 | - | 91.0 | 8.0 | 44.0 | - | 90.0 | 87.0 |
| Patient years | 673.2 | 347.5 | 344.7 | 361.3 | - | 742.9 | 5.6 | 40.0 | - | 55.6 | 427.3 |
| **Dataset 2 (OA trials of 12 mos)** | n=2952 | n=1519 | n=543 | n=550 | - | n=1845 | - | - | - | - | - |
| Mean | 230.4 | 229.0 | 248.7 | 254.9 | - | 243.3 | - | - | - | - | - |
| SD | 128.37 | 138.01 | 133.79 | 133.67 | - | 133.63 | - | - | - | - | - |
| Median | 272.0 | 268.0 | 320.0 | 355.5 | - | 279.0 | - | - | - | - | - |
| Patient years | 1862.1 | 952.4 | 369.7 | 383.8 | - | 1229.0 | - | - | - | - | - |
| **Dataset TARGET (OA trials of 12 mos)** | - | - | - | n=9117 | - | - | - | - | n= 4730 | n= 4397 | - |
| Mean | - | - | - | 275.7 | - | - | - | - | 272.9 | 256.7 | - |
| SD | - | - | - | 130.40 | - | - | - | - | 134.34 | 139.02 | - |
| Median | - | - | - | 361 | - | - | - | - | 361 | 358 | - |
| Patient years | - | - | - | 6881.6 | - | - | - | - | 3534.1 | 3090.0 | - |
| **Large integrated dataset** | | | | | | | | | | | |
| **Dataset 9 (OA+RA 1 wk - 12 mos)** | n=3895 | n=1712 | n=3245 | n=3075 | n=265 | n=3710 | n=771 | n=257 | n=681 | n=476 | n=3650 |
| Mean | 186.8 | 206.3 | 123.6 | 102.3 | 70.1 | 157.2 | 56.8 | 56.9 | 179.5 | 76.4 | 66.8 |
| SD | 136.69 | 144.78 | 116.27 | 100.16 | 29.70 | 128.89 | 39.15 | 25.17 | 112.13 | 26.59 | 42.64 |
| Median | 140.0 | 172.5 | 91.0 | 90.0 | 88.0 | 92.0 | 85.0 | 44.0 | 183.0 | 90.0 | 88.0 |
| Patient years | 1992.0 | 967.0 | 1098.1 | 861.3 | 50.9 | 1596.7 | 119.9 | 40.0 | 334.7 | 99.6 | 667.5 |

Includes treatments with mean exposure ≥50 days in any dataset. Patient years exposure calculated as n x (mean exposure in days/365.25)

## *Adverse events*

In all three dataset, representing short-term use, long-term use and use of higher doses, the most commonly affected classes were GI disorders, infections and infestations. Frequency of GI disorders was similar with lumiracoxib 100 mg od and celecoxib 200 mg od and increased with higher doses of lumiracoxib, confirming a dose related effect for GI safety.

In short-term OA studies of less than 13 week duration (Dataset 1), lumiracoxib 100mg od was not associated with a higher rate of AEs than comparators, except for the SOC 'Injury, poisoning and procedural complications'.

In long-term OA studies (Dataset 2, not TARGET), lumiracoxib 100mg od appears comparable with celecoxib 200mg od for common GI AEs. A dose-response is seen for GI, vascular and cardiac disorders for higher doses of lumiracoxib.

**Table 2-8 Common AEs (>=5% patients in any group) in OA long term studies (Dataset 2)**

| Primary system organ class<br>Preferred term | COX189 100mg od N=2952<br>n (%) | COX189 100mg bid N=1519<br>n (%) | COX189 200mg od N=543<br>n (%) | COX189 400mg od N=550<br>n (%) | Celecoxib 200mg od N=1845<br>n (%) |
|---|---|---|---|---|---|
| **Total** | **2031 (68.8)** | **1078 (71.0)** | **390 (71.8)** | **394 (71.6)** | **1208 (65.5)** |
| **Infections and infestations** | | | | | |
| Nasopharyngitis | 289 (9.8) | 141 (9.3) | 52 (9.6) | 41 (7.5) | 158 (8.6) |
| Upper respiratory tract infection | 142 (4.8) | 86 (5.7) | 15 (2.8) | 16 (2.9) | 66 (3.6) |
| Influenza | 126 (4.3) | 53 (3.5) | 23 (4.2) | 28 (5.1) | 62 (3.4) |
| **Gastrointestinal disorders** | | | | | |
| Diarrhea | 147 (5.0) | 55 (3.6) | 26 (4.8) | 32 (5.8) | 73 (4.0) |
| Dyspepsia | 123 (4.2) | 85 (5.6) | 30 (5.5) | 32 (5.8) | 94 (5.1) |
| Abdominal pain upper | 108 (3.7) | 88 (5.8) | 31 (5.7) | 34 (6.2) | 89 (4.8) |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Back pain | 183 (6.2) | 87 (5.7) | 28 (5.2) | 33 (6.0) | 109 (5.9) |
| Arthralgia | 162 (5.5) | 82 (5.4) | 28 (5.2) | 26 (4.7) | 81 (4.4) |
| **Nervous system disorders** | | | | | |
| Headache | 346 (11.7) | 174 (11.5) | 31 (5.7) | 42 (7.6) | 170 (9.2) |
| **Vascular disorders** | | | | | |
| Hypertension | 90 (3.0) | 48 (3.2) | 19 (3.5) | 35 (6.4) | 80 (4.3) |

All treatment groups are shown. Events are ordered in descending frequency in the COX189 100 mg od group

In TARGET, a large 1 year controlled GI outcomes study (n=18244) comparing lumiracoxib 400mg daily with ibuprofen 800mg tid and naproxen 500mg bid, AEs overall were comparable for the lumiracoxib group (79.3%) and naproxen or ibuprofen groups (78.6%, 80.9% respectively). In the TARGET subset of patients who consented to provided DNA for the pharmacogenetic sub-study, there is a reduced overall frequency of AEs in the non-carriers, 81.2% vs 84.0%, which may result in part from the reduced incidence of AEs resulting from hepatobiliary disorders and investigations.

### *Serious adverse events and deaths*

The overall frequency of SAEs with lumiracoxib 100 mg od was similar as compared to celecoxib 200 mg od. in both the short-term (up to 13 weeks) and longer-term (up to 1 year) datasets. Injury, poisoning, general disorders, nervous system disorders, GI disorders and musculoskeletal disorders all tended to become more frequent with rising lumiracoxib dose and were noticeably more common with prolonged treatment duration, in elderly and in patients with BMI <30 kg/m2. There was no obvious difference in the primary causes of death across different treatment groups. The most common cause of death in all groups was cardiac disorders.

In TARGET, there were 59 deaths overall, between start of treatment and database lock, of which 29 (0.3%) occurred in the Lumiracoxib 400mg od arm, 15 (0.3%) in the naproxen 500mg bid arm and 15 (0.3%) in the ibuprofen 800mg tid arm. The most common cause of deaths in all groups was cardiac disorders and the primary causes of death were generally similar across groups. The overall rates of SAEs were comparable between lumiracoxib 400mg od, ibuprofen 800mg tid and naproxen 500mg bid. There was an increase in musculoskeletal and connective tissue disorder, hepatobiliary disorder and nervous system disorder SAEs in the lumiracoxib groups compared to NSAIDs. However, apart for hepatobiliary, few disorders in these groups were attributed to lumiracoxib.

### *Laboratory findings*

For lumiracoxib 100mg od, the risk of a notable decrease in haemoglobin is similar to celecoxib and lower than traditional NSAIDs, consistent with a better GI safety profile. There were small increases in the rates of notable creatinine clearance reductions and notable creatinine increases for lumiracoxib relative to comparators, implying a less favourable renal safety profile. There were also increases in notable liver function test abnormalities for lumiracoxib relative to comparators (see section below on Liver Safety).

### *Gastrointestinal safety*

Gastrointestinal complications are a known drug class effect for NSAIDs.

The GI endpoints analysed were:

- POBs (upper GI perforation, obstruction, bleeding)
- PUBs (upper GI perforation, obstruction, bleeding and symptomatic ulcers)
- MedDRA terms defining pre-specified GI AEs

The risk of POBs and PUBs at 3 months for lumiracoxib 100mg od was lower than celecoxib 200mg od, but the risk of pre-specified AEs was higher. The 1 year estimated risks of POBs and pre-specified AEs were similar for lumiracoxib 100mg od and celecoxib 200mg od, and the risk of PUB for lumiracoxib was non-significantly lower. As with the 3 month data, the risks of POB and PUB with ibuprofen and naproxen were significantly higher compared to lumiracoxib.

TARGET was an international, multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, 52-week gastrointestinal clinical safety study which included 18325 patients. The risk of definite or probable upper gastrointestinal tract ulcer complications (POBs) was reduced by 79% (hazard ratio 0.21, 95% CI 0.12-0.37) with lumiracoxib 400mg od vs. NSAIDs in patients not taking low-dose aspirin, and by 66% (hazard ratio 0.34, 95% CI 0.22-0.52) in the overall population. In patients taking low dose aspirin, the incidence was numerically lower with lumiracoxib but the reduction was not statistically significant (the study was not powered to show a difference in this sub-group).

### *Cardiovascular safety*

In 2004, cardiovascular events from a number of clinical trials resulted in the withdrawal of rofecoxib and heightened concerns over the cardiovascular safety of the entire COX-2 inhibitor class. In November 2004, the European Commission referred this class of drugs for European-wide assessment by the Committee on Human Medicinal Products (CHMP) under Articles 18 and 31 of Directive 2001/83/EC.

Evaluation of the cardiovascular safety of lumiracoxib was based on a standard meta-analysis and a cumulative meta-analysis including data from the TARGET study.

The TARGET study was prospectively adjudicated and was able to measure coronary events (myocardial infarction [both clinical and silent], unstable angina, cardiac arrest, cardiovascular death), cerebrovascular events (stroke [both ischemic and hemorrhagic], transient ischemic attack), deep vein thrombosis and pulmonary embolism. TARGET included more than 2200 patients with a CV history or high CV risk based on Framingham risk equations. The data on lumiracoxib in the TARGET study suggests a small increase in thrombotic events (especially myocardial infarction) versus naproxen.

In the complete dataset (D9+TARGET), crude rates for CV endpoints (APTC, congestive heart failure, pre-specified CV AEs) show rates for lumiracoxib that were similar to comparators and slightly increased compared to placebo. There was a trend towards an increase for higher lumiracoxib doses. For lumiracoxib 100mg od, the calculated odds ratios at one year showed a slightly higher risk of MI and lower risk of stroke relative to comparators. The APTC endpoints were comparable.

In June 2005 the CHMP adopted an opinion in which it was concluded that all available data showed an increased risk of CV adverse reactions for COX-2 inhibitors as a class and that there is an association between duration and dose of intake and the probability of suffering a CV reaction. The CHMP requested changes to the SPC and that the cardiovascular safety should be continuously and carefully monitored and assessed. Adequate warnings have been included in the proposed SPC by the applicant.

### *Renovascular safety*

Renal events are known drug class effects.

Renal effects were evaluated in terms of:

- post-baseline elevation of creatinine >1.5 x ULN
- creatinine increase from baseline >0.4 mg/dL
- creatinine clearance decrease from baseline >25%

Using the 12 month database, the risk of creatinine increase and creatinine clearance decrease was higher for lumiracoxib 100mg od relative to celecoxib 200mg od, naproxen 500mg bid and ibuprofen 800mg tid. However the rates of renal SAEs were similar to comparators.

The estimated 3 month risks of BP rise and oedema for lumiracoxib 100mg were similar to comparators, except ibuprofen, for which rates were higher. At 12 months, the rates of hypertension and oedema AEs remained favourable for lumiracoxib 100mg relative to comparators.

Study 2428 was a 4 week, double-blind study comparing ambulatory blood pressure in controlled hypertensive patients treated with lumiracoxib 100 mg od or ibuprofen 600 mg tid for OA. The following table shows that the change from baseline in mean systolic blood pressure, using the primary analysis and sensitivity analyses to take account of missing data, which are acceptable:

**Table 3-3 Change from baseline in 24h MASBP at week 4 (primary analysis and analysis of all randomised patients using missing data imputation)**

| Imputation method (Analysis dataset) Treatments | N | LS means(SE) | Estimated difference (SE) | 95% CI of difference | p-value** |
|---|---|---|---|---|---|
| **No imputation (original primary analysis)** | | | | | |
| Lumiracoxib 100 mg od | 363 | -2.7 (0.43) | **-5.0** (0.56) | -6.1, -3.8 | **<0.001**** |
| Ibuprofen 600 mg tid | 359 | 2.2 (0.44) | | | |
| **Method 1 (All randomized patients)** | | | | | |
| Lumiracoxib 100 mg od | 394 | -2.3 (0.41) | **-4.4** (0.53) | -5.5, -3.4 | **<0.001** |
| Ibuprofen 600 mg tid | 393 | 2.2 (0.40) | | | |
| **Method 2 (All randomized patients)** | | | | | |
| Lumiracoxib 100 mg od | 394 | -2.6 (0.40) | **-4.4** (0.52) | -5.4, -3.4 | **<0.001** |
| Ibuprofen 600 mg tid | 393 | 1.8 (0.40) | | | |
| **Method 3 (All randomized patients)** | | | | | |
| Lumiracoxib 100 mg od | 394 | -2.3 (0.41) | **-4.0** (0.53) | -5.1, -3.0 | **<0.001** |
| Ibuprofen 600 mg tid | 393 | 1.8 (0.41) | | | |
| **Method 4 (All randomized patients)** | | | | | |
| Lumiracoxib 100 mg od | 394 | -2.4 (0.40) | **-4.4** (0.52) | -5.5, -3.4 | **<0.001** |
| Ibuprofen 600 mg tid | 393 | 2.2 (0.40) | | | |

Missing baseline MASBP data were imputed
** ANCOVA with treatment as main effect, center and baseline 24h MASBP as covariates. Pairwise comparison tested at the 5% significance level, lumiracoxib 100 mg od vs. ibuprofen 600 mg tid
*** LS means (SE) = least squares means (standard error) for change from baseline
**** Source: [2428 - PT-Table 14.2-1.5]
Source: [Appendix 4 - Table E 14.2.2-27]

The change in mean ambulatory diastolic blood pressure was 2.0 mmHg lower in the lumiracoxib arm. In addition, all secondary analyses of ambulatory blood pressure showed a statistically significant superior result for the lumiracoxib group. However it should be noted that although the results demonstrate that change in blood pressure during treatment with lumiracoxib was significantly less than for ibuprofen, they do not support the claim that lumiracoxib decreases blood pressure.

### *Safety in special populations*

There are no implications for the use of lumiracoxib on the basis of gender, age or body weight. However, there is highly limited information on the pharmacokinetics in subjects older than 75 years of age. The applicant will be asked to state this in Section 4.2 of the SPC. Studies have not been conducted in children, and use is contraindicated. No studies have been carried out in pregnant or lactating women.

There was no difference in exposure between normal subjects and subjects with moderate hepatic impairment (Child-Pugh score 7 to 9). The SPC proposal is for lumiracoxib to be contraindicated in patients with any current hepatic disease; a history of clinically significant liver disease, including patients with prior drug-induced significant (> 5x ULN or persistent > 3x ULN) elevations of transaminases; patients with liver transaminases > 1.0 x ULN before treatment.

Exposure to lumiracoxib metabolites is increased in mild and moderate renal impairment. There is an SPC proposal to contraindicate for patients with CrCl < 50ml/min, which is acceptable.

Lumiracoxib PK is not affected to a clinically significant degree by ethnic group. However, a major outstanding issue remains relating to the use of the DQA1*0102 screening test in non-Caucasians (see Section 5).

### *Immunological events*

Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving lumiracoxib. In placebo/active-controlled OA clinical studies up to one year hypersensitivity events were reported in 23/1771 patients with 100 mg od (1 yr Kaplan-Meier risk, 1.50%) and 159/9667 patients with 400 mg od (1 yr Kaplan-Meier risk, 1.91%). For celecoxib 200mg od 17/1845 patients had hypersensitivity events.

Serious cutaneous adverse reactions, (SCARs) some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy.

In placebo/active-controlled OA clinical studies up to one year SCAR events were reported in 2/1771 patients with 100 mg od (1 yr Kaplan-Meier risk, 0.12%) and 14/9667 patients with 400 mg od (1 yr Kaplan-Meier risk, 0.17%). For celecoxib 200mg od 3/1845 patients had SCAR events.

No cases of Stevens Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme were reported with lumiracoxib in any clinical study, conditions that have been reported with other NSAIDs.

In June 2005 the CHMP scientific conclusions on this issue were announced which concluded that lumiracoxib does not appear to be associated with an unusually large number of reports of serious skin reactions. There were no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme reported in association with the use of lumiracoxib in clinical trials. The CHMP requested changes of the Product Information related to SCAR. A general text adequately describing immunological events has been included in the SPC, by the applicant.

### *Safety related to drug-drug interactions and other interactions*

An increase in prothrombin time has been demonstrated with the concomitant use of warfarin and lumiracoxib (study 0134). The known and theoretical pharmacodynamic interactions are dealt with adequately in section 4.5 of the SPC.

Clinical pharmacology studies have found no evidence of PK interaction with fluconazole (a potent CYP2C9 inhibitor), omeprazole (a CYP2C19 inhibitor), antacids, warfarin, low dose methotrexate, and oral contraceptives. An interaction with high dose methotrexate (decreased renal clearance of methotrexate) cannot be excluded. An influence by opioids on the gastric emptying was observed, resulting in approximately 50 % decreased absorption. *In vitro* protein-binding studies suggest that clinically significant interactions as a result of displacement are unlikely. There is a possibility for inhibition by lumiracoxib on CYP2C9 substrates, however is likely not clinically significant other than for CYP2C9 substrates with narrow therapeutic index. The applicant will be asked to add the data from the interaction observed with opioids to Section 4.5 of the SPC.

### *Discontinuation due to AES*

Rates of AE discontinuations overall at 13 weeks (D1) were no higher with lumiracoxib 100 mg od than placebo. Overall more than 3 times more patients taking ibuprofen had AEs leading to discontinuation as compared to lumiracoxib 100mg od (12.7% vs. 4.1%, respectively). GI disorders and investigations were the most common reason leading to discontinuation in patients with ibuprofen.

Rates of AE discontinuations overall at 52 weeks (D2) were numerically less with lumiracoxib 100 mg od compared to celecoxib, mostly for nervous system, psychiatric and cardiac event. With increasing dose of lumiracoxib the rate of discontinuations rose and exceeded the rates for celecoxib.

### *Post marketing experience*

The applicant has provided copies of PSURs (plus bridging report and an addendum report) covering the period from 13 Sep 2003– 30 Sep 2009. Cumulatively 66 reports with a fatal outcome were received from spontaneous reports. The submitted post-marketing data is broadly consistent with the known effects of lumiracoxib. A number of issues should remain under close review in future PSURs.

### *Liver safety*

During the clinical studies, 11 lumiracoxib patients met Hy's Law criteria (ALT/AST ≥ 3x ULN and total bilirubin ≥ 2x ULN), all at doses higher than 100mg od. Hy's Law cases are associated with 10-50% risk of death or transplant.

For lumiracoxib 100mg od, the crude rates and risks estimates for transaminase rises at 3 months were below or similar to comparators or placebo. However, by 12 months, crude rates were higher for lumiracoxib relative to comparators for all categories of transaminase elevation, as shown below:

| Rise above ULN | LUM 100mg od N=1845 | CEL 200mg od N=1845 | NAP 500mg bid N=4730 | IBU 800mg tid N=4397 |
|---|---|---|---|---|
| | Crude rates over 12 months - % (n) | | | |
| ALT/AST >3xULN | **1.19** (21) | **0.60** (11) | **0.44** (24) | **0.80** (35) |
| ALT/AST >5xULN | **0.40** (7) | **0.05** (1) | **0.11** (6) | **0.30** (13) |
| ALT/AST >8xULN | **0.28** (5) | **0.05** (1) | **0.06** (3) | **0.09** (4) |
| ALT/AST >10xULN | **0.06** (1) | **0.05** (1) | **0.02** (1) | **0.05** (2) |
| | Risk estimates for 12 months - % (95% CI) | | | |
| ALT/AST >3xULN | **1.63** (0.9, 2.3) | **0.65** (0.3, 1.0) | **0.57** (0.3, 0.8) | **1.04** (0.7, 1.4) |
| ALT/AST >5xULN | **0.54** (0.1, 0.9) | **0.07** (0.0, 0.2) | **0.17** (0.0, 0.3) | **0.38** (0.2, 0.6) |
| ALT/AST >8xULN | **0.38** (0.2, 0.6) | **0.07** (0.0, 0.2) | **0.09** (0.0, 0.2) | **0.12** (0.0, 0.2) |
| ALT/AST >10xULN | **0.07** (0.0, 0.2) | **0.07** (0.0, 0.2) | **0.03** (0.0, 0.1) | **0.06** (0.0, 0.2) |
| | Odds ratio relative to LUM 100 mg od for 12 months | | | |
| ALT/AST >3xULN | - | **0.40** | **0.34** | 0.64 |
| ALT/AST >5xULN | - | 0.14 | **0.32** | 0.70 |
| ALT/AST >8xULN | - | 0.19 | **0.23** | 0.31 |
| ALT/AST >10xULN | - | 0.99 | 0.36 | 0.80 |

Dataset 12r = double-blind, 52 week OA studies
LUM = lumiracoxib, CEL = celecoxib, NAP = naproxen, IBU = ibuprofen
odds ratios in bold are statistically significantly different from 1

In the TARGET study, the proportion of patients with ALT/AST > 3 x ULN (adjudicated by an independent Liver Safety Committee as probably or possibly related to study drug was 2.6% (lumiracoxib 400mg od) vs 0.6% (NSAIDs – naproxen and ibuprofen arms combined).

The 3 month database (D1) shows similar rates of hepatic events for lumiracoxib compared to comparators. However in the longer term databases, an increased rate is seen, even for the 100mg dose. There appears to be time dependency for the rates of hepatic events, with a sharp increase between 3-6 months.

No Hy's Law cases have been reported in the clinical trials at 100mg od. However there were 7 cases of >5x ULN AST/ALT, at which point the patient would be immediately discontinued. It is therefore possible that in clinical trials, insufficient patients were exposed to 100mg lumiracoxib for long enough to detect rare events of concomitant AST/ALT/ bilirubin increases and subsequent hepatic failure.

As of 30 Sep 2009, review of the post-marketing spontaneous reports of hepatic disorders revealed 24 severe hepatic cases based on the following criteria (1) case with reported term "hepatic failure"; or (2) confirmed Hy's case (i.e. ALT/AST > 3 x ULN and bilirubin > 2 x ULN); or (3) case with outcome death or transplant. 10 cases have been reported for 100mg od, of which there has been 1 death and 1 transplant.

Following post marketing reports of severe/serious cases of hepatotoxicity, the CHMP started a safety review under Articles 107 of Directive 2001/83/EC, which announced the following decision:

*"Lumiracoxib is indicated for the symptomatic relief of a non-serious disease condition, where there are alternatives available including options with a comparable GI profile as lumiracoxib (another coxib or NSAID + PPI). It is not considered that the identified hepatic risk as it appears today is outweighed by the benefit of lumiracoxib. Given that no risk minimisation activity can be identified that would ensure that the risk for hepatic reactions is sufficiently reduced, a revocation of the marketing authorisation is recommended"*

Consequently, the EU Commission recommended revocation of national marketing authorizations on 6-March-2008.

The company has now submitted data from a retrospective case-control genome-wide association study using DNA samples collected from 10,057 patients enrolled in the TARGET study. The genetic sub-study, conducted in 137 cases with hepatotoxicity and 577 matched controls, has led to the identification of a genetic biomarker (DQA1*0102 allele in the MHC Class II region), which may predict patients potentially at risk of developing lumiracoxib-associated hepatotoxicity.

### *Pharmacogenetic sub-study of TARGET (0117-2332ad1)*

The primary objective was to identify genetic markers associated with an increased risk of developing elevated liver enzymes after treatment with lumiracoxib. A case-control study design was used throughout. Cases were lumiracoxib-treated patients with transaminase rises. Controls were lumiracoxib-treated patients without biochemical liver abnormalities.

The TARGET studies 0117 and 2332 were randomised, double-blind, double-dummy, parallel group, 52 week gastrointestinal safety studies in OA patients ≥50 years. The primary aim was to demonstrate that lumiracoxib 400mg od reduced the risk of developing complicated ulcers as compared to NSAIDs (naproxen 500mg bid and ibuprofen 800mg tid). It was found that the proportion of patients with ALT/AST > 3 x ULN (adjudicated by an independent Liver Safety Committee as probably or possibly related to study drug) was 2.6% (lumiracoxib 400mg od) vs 0.6% (NSAIDs – naproxen and ibuprofen arms combined).

During the main TARGET studies, DNA samples were prospectively collected from 10,057 consenting study patients out of a total of 18,244 randomised. Of the 10,057 providing DNA, 4518 received lumiracoxib 400mg od Using this sub-population the study was conducted in 4 Stages:

- Exploratory genome-wide association study
- Replication and extension of exploratory results
- Identification of associated HLA genes and alleles
- Identification of additional markers

An exploratory genome-wide association study

An initial case-control exploratory whole genome association study was conducted in patients receiving lumiracoxib, using 41 patients with ALT/AST >5xULN, matched to 176 controls. A large peak of associated SNPs was observed on chromosome 6 with rs9270986 yielding the most significant result (p=2.8x10-10, followed by rs3129900, p=1.8x10-9). The majority of the SNPs under this peak were located in the extended MHC region with the most significant findings mapping to the MHC class II region. A total of 7 SNPs were still statistically significant (p<0.05) after correcting for multiple testing. The permutation test used to adjust for multiple testing is considered acceptable.

Replication and extension of exploratory results

The most significant single nucleotide polymorphisms (SNPs) from the genome-wide scan and other high-ranking SNPs in potentially relevant genes were replicated in an independent set of 98 lumiracoxib-treated patients with >3x ULN AST/ALT matched to 405 lumiracoxib-treated controls. The results of the replication study are shown below, with several of the top SNPs in the MHC class II region strongly replicating. The most significant result was for rs3129900 (p=4.4x10-12). None of the non-HLA SNPs showed any statistical evidence of association.

**Replication study results (>3xULN ALT/AST)**

| rs number | Gene/ region | HWE p-value | p-value | MAF cases | MAF controls | Carrier case frequency | Carrier control frequency |
|---|---|---|---|---|---|---|---|
| 9270986 | MHC | 0.17 | $1.0x10^{-9}$ | 34.5% | 14.8% | 59.8% | 26.9% |
| 3129900 | MHC | 0.71 | $4.4x10^{-12}$ | 36.7% | 14.8% | 61.2% | 27.3% |
| 3129934 | MHC | 0.72 | $4.9x10^{-11}$ | 36.3% | 14.9% | 61.1% | 27.6% |
| 3135365 | MHC | 0.40 | $6.3x10^{-10}$ | 39.8% | 18.8% | 66.3% | 33.8% |
| 2517538 | MHC | 0.63 | 0.084 | 45.8% | 38.6% | 69.5% | 62.0% |
| 3130952 | MHC | 0.087 | $4.5x10^{-4}$ | 21.4% | 11.9% | 36.5% | 21.9% |
| 9275772 | MHC | 0.17 | $2.6x10^{-6}$ | 36.2% | 20.7% | 58.2% | 35.7% |
| 2517451 | MHC | 0.53 | 0.0018 | 15.5% | 8.5% | 27.8% | 16.6% |
| 10509681 | CYP2C8 | 0.17 | 0.099 | 14.1% | 9.8% | 26.0% | 18.1% |
| 2577302 | FN1 | 0.53 | 0.47 | 4.1% | 3.2% | 8.2% | 6.4% |
| 7131977 | ALDH1L2 | 0.41 | 0.56 | 7.2% | 6.2% | 14.4% | 11.9% |
| 9659646 | chr. 1 | 0.89 | 0.66 | 1.0% | 0.8% | 2.1% | 1.5% |
| 2123139 | chr. 11 | 0.28 | 0.48 | 4.2% | 5.5% | 8.4% | 10.9% |

HWE= Hardy-Weinberg Equilibrium, MAF= Minor Allele Frequency

Two of the 15 assays of polymorphisms chosen to replicate the top genome-wide screen findings (based on the initial genome wide association study) failed in the independent sample of cases and controls, and 13 polymorphisms successfully genotyped were included in the analysis. The genotyping

failure of rs3132943 and rs3132611 is not considered to have any effect on the development of the genetic biomarker. Although statistical significance was not reached, there was a higher frequency of rs10509681 in CYP2C8 gene in cases (26%) than in controls (18.1%). There was no evidence of association between the SNP associated with the CYP2C9*3 allele and hepatotoxicity, in the initial exploratory phase.

Exploratory analysis of top SNPs in comparator arm (naproxen and ibuprofen) for cases with elevated liver enzymes (>3xULN ALT/AST)

The 13 SNPs tested in the replication study were also tested for association with liver enzyme elevation (>3xULN ALT/AST) in the TARGET comparator arms. Cases (n=18 ibuprofen; n=9 naproxen) were matched to controls using the same criteria and ratio as described earlier. No results were significant after adjusting for multiple testing across the SNPs (n=13) evaluated in this comparator arm analysis when examined either individually or as combined arms. The only result to reach nominal significance ($p < 0.05$) was for SNP rs3130952 in the naproxen-treated patients ($p= 0.015$). This SNP is located in the HLA Class I region and is only weakly correlated with DQA1*0102. There is no evidence to suggest that DQA1*0102 carriers are at increased risk of hepatotoxicity from treatment with naproxen or ibuprofen, compared to the general population.

Identification of associated HLA genes and alleles

A genetic fine mapping study of HLA genes neighbouring the candidate SNPs was undertaken in order to identify potentially causative polymorphisms in the MHC class II region. The genotyping of HLA alleles was performed for HLA-DRB1, HLA-DRB3-5, HLA-DQA1, and HLA-DQB1.

HLA genotyping and analysis of all cases (n=137) and controls (n=577) was performed and a strong association to a well characterized HLA haplotype (DRB1*1501-DQB1*0602-DRB5*0101-DQA1*0102) was identified. Of these the DRB1*1501 allele was found to be the most strongly associated with hepatotoxicity in lumiracoxib-treated patients (p=6.8x10-25). However, for potential markers of safety the parameters of greatest interest are negative predictive value (NPV) and sensitivity.

The marker with the best results for these parameters is DQA1*0102 with an NPV of 99.03% and a sensitivity of 73.7% for >3xULN ALT/AST. The DQA1*0102 marker's predictive performance was found to be greatest in the most severe cases, with an NPV of 99.94% and a sensitivity of 91.7% for >10xULN ALT/AST.

**Most significant HLA genes and alleles associated with elevated liver enzymes (>3xULN ALT/AST): (137 cases and 577 controls)**

| Gene/allele | p-value |
|---|---|
| DRB1*1501 | $6.8x10^{-25}$ |
| DQB1*0602 | $1.1x10^{-22}$ |
| DRB5*0101 | $1.6x10^{-20}$ |
| DQA1*0102 | $1.2x10^{-18}$ |

Extension of DQA1 genotyping to all available lumiracoxib treated patients

Genotyping of the DQA1 gene was then performed on all remaining patients in the TARGET study who provided DNA and informed consent for the pharmacogenetic study, resulting in an additional 3804 successfully genotyped patients with liver enzyme measurements taken after treatment with lumiracoxib. Combining this sample with the 714 patients successfully genotyped for the DQA1*0102

allele in the case/control analysis yielded a total of 4518 lumiracoxib-treated patients available for analysis. The extrapolation to the full target population was required in order to provide a better estimation of the predictive parameters in a population which had not been enriched in terms of the number of cases as for the initial association testing. When considering the estimates of the negative and positive predicted values presented in the original report, it is important to note that they are based on the assumption that the non-genotyped patients had the same carrier frequencies of the allele as the corresponded genotyped matched patients for both cases and controls.

**Predictive parameters, including 95% confidence intervals for DQA1*0102 using all available TARGET patients (n=4518):**

| ALT/AST elevation threshold | Sensitivity | Specificity | PPV | NPV | RR | Allele frequency case/control |
|---|---|---|---|---|---|---|
| >3xULN | 73.6% (65.5-80.7%) | 67.7% (66.3-69.1%) | 5.6% (5.0-6.2%) | 99.00% (98.68-99.24%) | 5.6 | 43.2%/17.8% |
| >5xULN | 84.1% | 67.7% (66.3-69.1%) | 3.1% (2.8-3.5%) | 99.71% (99.49-99.84%) | 10.8 | 50.0%/17.8% |
| >8xULN | 91.2% | 67.7% (66.3-69.1%) | 1.7% (1.5-1.9%) | 99.92% (99.76-99.97%) | 21.3 | 52.9%/17.8% |
| >10xULN | 92.0% | 67.7% (66.3-69.1%) | 1.4% (1.2-1.6%) | 99.94% (99.78-99.98%) | 23.8 | 54.0%/17.8% |

PPV = positive predictive value, NPV = negative predictive value, RR = relative risk

For patients with lumiracoxib-related hepatotoxicity the DQA1*0102 marker's predictive performance was found to be greatest in the most severe cases.

**Sensitivity and number of cases with the DQA1*0102 allele as a function of severity of liver enzyme (ALT/AST) elevation**

| ULN ALT/AST | Sensitivity | Number of cases with DQA1*0102 allele | Total number of genotyped cases |
|---|---|---|---|
| >3x | 73.6% | 103 | 140 |
| >5x | 84.1% | 53 | 63 |
| >8x | 91.2% | 31 | 34 |
| >10x | 92.0% | 23 | 25 |
| >15x | 94.1% | 16 | 17 |
| >20x | 100% | 8 | 8 |

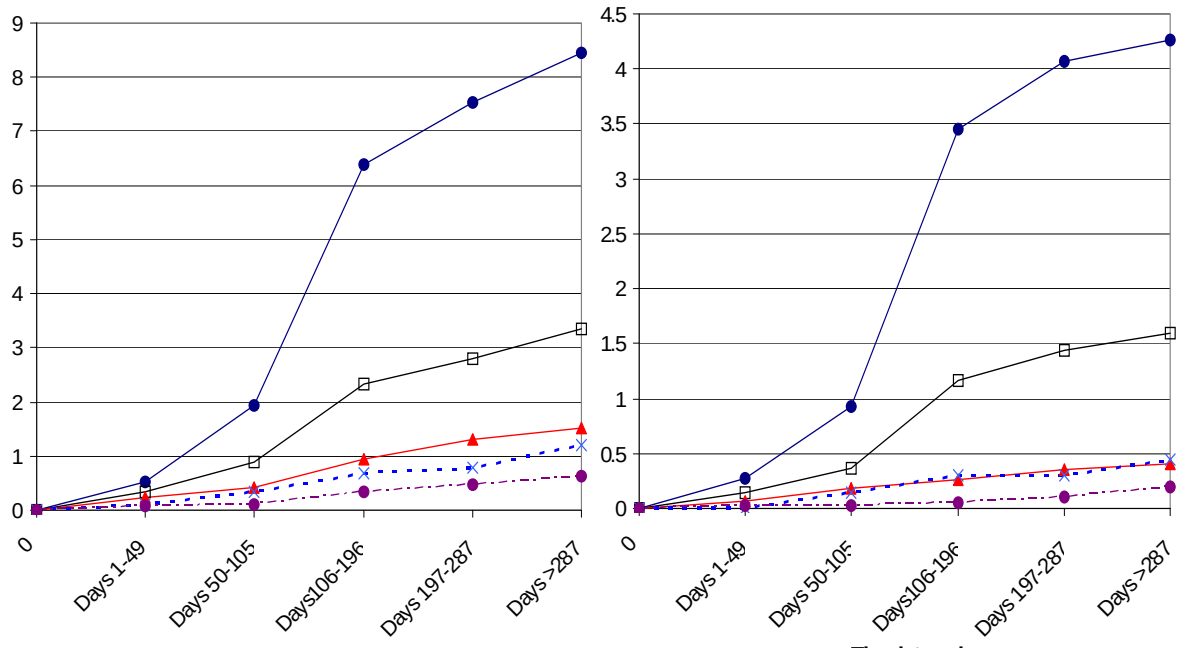
Liver enzyme (ALT/AST) elevation rates in TARGET

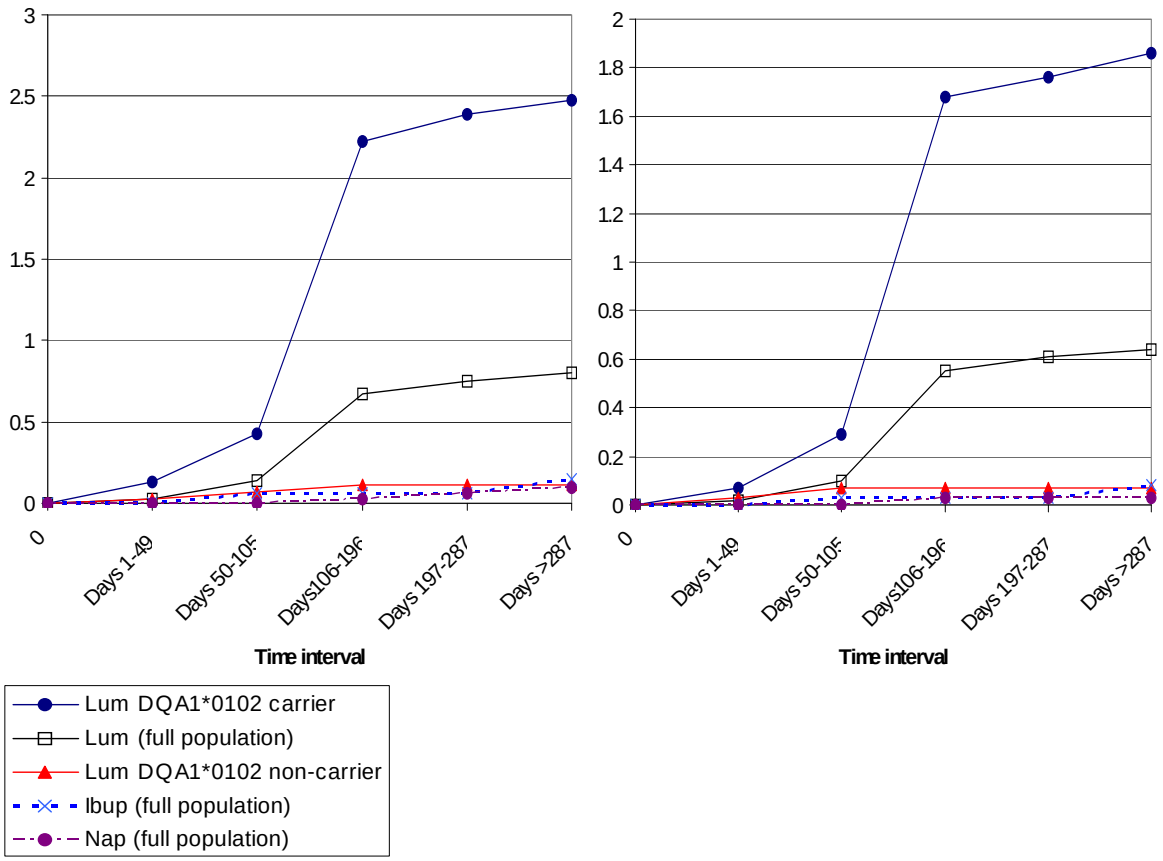
Compared to the lumiracoxib arm as a whole, the crude rates for ALT/AST elevations in lumiracoxib DQA1*0102 non-carrier patients were reduced. Crude rates of ibuprofen and naproxen are provided for comparison. Given the 95% confidence intervals for the DQA1*0102 predictive parameters, it is possible that the actual rate of > 3x ULN AST/ALT in the non-carrier population could be higher than the crude rate of 1.23% in TARGET.

**Liver enzyme (ALT/AST) elevation crude rates in TARGET**

| Treatment group | N | ALT/AST >3xULN n (%) | ALT/AST >5xULN n (%) | ALT/AST >8xULN n (%) | ALT/AST >10xULN n (%) | ALT/AST >3xULN + bilirubin ≥2xULN n (%) |
|---|---|---|---|---|---|---|
| Lumiracoxib | 9117 | 230 (2.52%) | 111 (1.22%) | 56 (0.61%) | 45 (0.49%) | 9 (0.10%) |
| Lumiracoxib DQA1*0102 carriers | 1518 | 103 (6.79%) | 53 (3.49%) | 31 (2.04%) | 23 (1.52%) | 3 (0.20%) |
| Lumiracoxib DQA1*0102 non-carriers | 3000 | 37 (1.23%) | 10 (0.33%) | 3 (0.10%) | 2 (0.07%) | 0 (0.00%) |
| Ibuprofen | 4397 | 35 (0.80%) | 13 (0.30%) | 4 (0.09%) | 2 (0.05%) | 2 (0.05%) |
| Naproxen | 4730 | 21 (0.44%) | 6 (0.13%) | 3 (0.06%) | 1 (0.02%) | 2 (0.04%) |

**Figure 1**
**Cumulative Kaplan-Meier rates (%) for transaminase elevations >3x, >5x ULN (top left, right), >8x, >10xULN (lower left, right), OA TARGET**

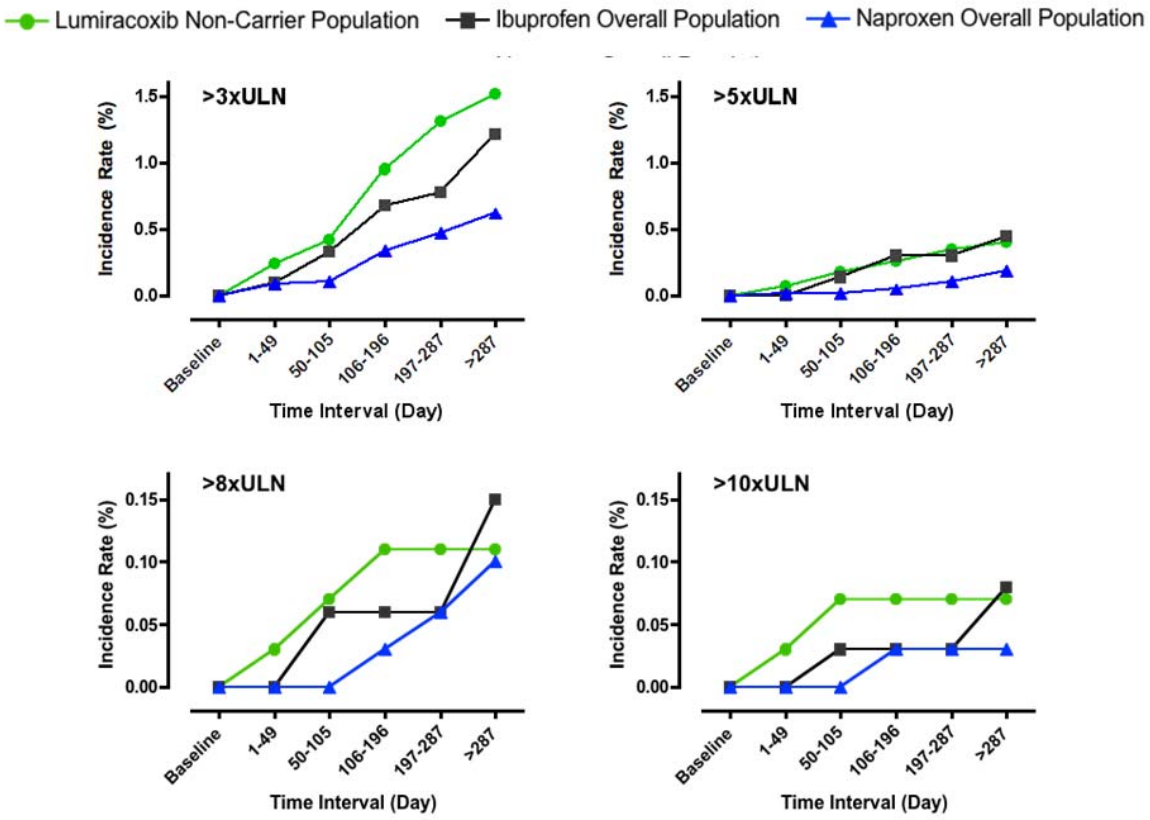





The following figure shows the same K-M estimates with exclusion of the lumiracoxib carrier and full populations. There appears to be an excess of >3x ULN ALT/AST cases in lumiracoxib non-carriers compared to ibuprofen and naproxen.

:

**Figure** Error! No text of specified style in document. **Kaplan-Meier estimates for ALT/AST elevations in non-carriers taking lumiracoxib 400 mg od and all patients taking ibuprofen or naproxen (TARGET)**

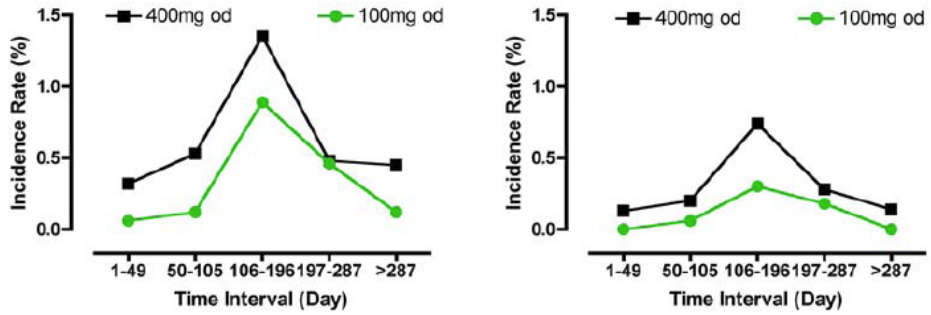



Source: TARGET pharmacogenetic sub-study [COX189A 0117-2332ad1 - Table 3.2-1 to Table 3.2-4].

An increase in the incidence in lumiracoxib-related ALT/AST elevations in DQA1*0102 carriers has been noted during the days 106-196 time interval, which suggests that the HLA-driven liver toxicity does not manifest clinically until after several weeks of exposure to lumiracoxib. This seems to be different from the situation in non-carriers which do not show a sharp increase at this time interval. A similar time to event pattern is noted for all 400mg and 100mg daily lumiracoxib cases, as shown in Figure 2-1 below:

**Figure 2-1 Incidence rate of AST/ALT increases (probably/possibly lumiracoxib-related) over time (Dataset 12r)**

a. >3x ULN b. >5x ULN




Source: [SCS Appendix 5 (Liver)-Table 2-1.2 and Table 2-2.2]

However, it should be noted that the X-axis is not linear, and that the point 106-196 represents 2 liver function monitoring visits, compared to one visit for the other timepoints.

The Applicant has performed an exploratory analysis using Bayesian Network (BN) algorithm using genotyped patients from the TARGET study to attempt to identify non-genetic risk factors. The only variable yielding strong evidence of association was ALT and/or AST levels >1xULN at screening. Based on this finding, a new 2-factor predictive model was evaluated assuming that all patients carrying the DQA1*0102 allele or having ALT/AST >1xULN at screening would be excluded from treatment with lumiracoxib.

By excluding about 10% of the DQA1*0102 non-carrier with ALT/AST >1xULN at screening, the predictive parameters (sensitivity, specificity, PPV, and NPV) were somewhat improved. However, the improvement in predictive values by using the 2-factor predictive model is not apparent for the lumiracoxib 100mg treated patients, as shown highlighted in Table 1-19 below.

**Table 1-19 AST/ALT elevations (crude rates, 1 yr K-M estimates) with and without patients above ULN at baseline (All races)**

| | LUM 400 mg od * All genotyped | | LUM 400 mg od * Non-carriers | | LUM 100 mg od ** | | IBU * ** | | NAP * ** | | CEL ** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All** N=4518 n (%) | **≤ULN** N=4035 n (%) | **All** N=3000 n (%) | **≤ULN** N=2674 n (%) | **All** N=1771 n (%) | **≤ULN** N=1596 n (%) | **All** N=4397 n (%) | **≤ULN** N=3927 n (%) | **All** N=4730 n (%) | **≤ULN** N=4246 n (%) | **All** N=1845 n (%) | **≤ULN** N=1636 n (%) |
| Crude rates (%, bold) and numbers of events | | | | | | | | | | | | |
| >3xULN | 3.10 | 2.65 | 1.23 | 0.90 | 1.19 | 1.19 | 0.80 | 0.61 | 0.44 | 0.40 | 0.60 | 0.24 |
| | 140 | 107 | 37 | 24 | 21 | 19 | 35 | 24 | 21 | 17 | 11 | 4 |
| >5xULN | 1.39 | 1.14 | 0.33 | 0.19 | 0.40 | 0.38 | 0.30 | 0.28 | 0.13 | 0.12 | 0.05 | |
| | 63 | 46 | 10 | 5 | 7 | 6 | 13 | 11 | 6 | 5 | 1 | 0 |
| >8xULN | 0.75 | 0.59 | 0.10 | 0.04 | 0.28 | 0.25 | 0.09 | 0.10 | 0.06 | 0.07 | 0.05 | |
| | 34 | 24 | 3 | 1 | 5 | 4 | 4 | 4 | 3 | 3 | 1 | 0 |
| >10xULN | 0.55 | 0.40 | 0.07 | 0.04 | 0.06 | | 0.05 | 0.05 | 0.02 | 0.02 | 0.05 | |
| | 25 | 16 | 2 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 0 |
| Kaplan-Meier estimates (%, bold) and 95% CIs | | | | | | | | | | | | |
| >3xULN | 3.83 | 3.31 | 1.52 | 1.14 | 1.81 | 1.83 | 1.21 | 0.92 | 0.62 | 0.56 | 0.72 | 0.30 |
| | 3.20, 4.46 | 2.74, 4.00 | 1.03, 2.01 | 0.76,1.71 | 1.03, 2.59 | 1.16, 2.87 | 0.80, 1.62 | 0.61, 1.39 | 0.35, 0.89 | 0.34, 0.90 | 0.29,1.15 | 0.11, 0.82 |
| >5xULN | 1.69 | 1.39 | 0.40 | 0.23 | 0.60 | 0.59 | 0.45 | 0.43 | 0.19 | 0.19 | 0.08 | 0 |
| | 1.28, 2.11 | 1.04, 1.85 | 0.15, 0.64 | 0.09,0.55 | 0.15, 1.06 | 0.26, 1.31 | 0.20, 0.70 | 0.23, 0.79 | 0.03, 0.34 | 0.08, 0.45 | 0.00, 0.22 | |
| >8xULN | 0.91 | 0.72 | 0.11 | 0.04 | 0.41 | 0.37 | 0.15 | 0.17 | 0.10 | 0.12 | 0.08 | 0 |
| | 0.60, 1.21 | 0.48, 1.07 | 0.00, 0.24 | 0.01, 0.30 | 0.05, 0.77 | 0.14, 1.00 | 0.00, 0.31 | 0.06, 0.47 | 0.00, 0.22 | 0.04, 0.37 | 0.00, 0.23 | |
| >10xULN | 0.67 | 0.48 | 0.07 | 0.04 | 0.08 | 0 | 0.08 | 0.09 | 0.03 | 0.03 | 0.08 | 0 |
| | 0.41, 0.93 | 0.29, 0.78 | 0.00, 0.17 | 0.01, 0.30 | 0.00, 0.22 | | 0.00, 0.20 | 0.02, 0.39 | 0.00, 0.08 | 0.00, 0.21 | 0.00, 0.23 | |

*TARGET, **Dataset 12r , ULN= upper limit of normal, for ≤ ULN at baseline those patients with missing baseline values were excluded
Source: EMA Response Tables 2.1-4.12r, 2.3-1.12r, 2.3-4.12r, 2.3-7-12r, 2.3-10.12r, 2.4-3.1, 2.4-4.1, 2.4-4.2, 2.4-4.3, [SCS Appendix 5 Tables 2-1.2, 2-2.2, 2-3.2, 2-4.2], [SCS Appendix 7 Table 1.3.Dataset D12r], TARGET Pharmacogenetic Addendum Tables 3.1-1, 3.2-1, 3.2-2, 3.2-3, 3.2-4

Nine Hy's law cases were reported in the lumiracoxib arms of TARGET but only 3 were used in the pharmacogenetic analysis: all were heterozygous for DRB1*1501, DRB5*0101 and DQA1*0102 alleles. No DNA or informed consent was obtained for 5 of the remaining cases, while the 6th case was not successfully genotyped. The Applicant has provided follow-up data for these cases (see Study 2483 below). The case not successfully genotyped was subsequently found to be a DQA1*0102 carrier. Of the 5 who did not originally provide DNA, 2 are deceased, and 3 have been tested and are carriers.

There is no evidence of association of DQA1*0102 and hepatotoxicity in ibuprofen or naproxen arms.

DQA1*0102 Marker performance in the European region (including South Africa)

The DQA1*0102 marker's performance in patients from European study centres was examined. A total of 2049 lumiracoxib-treated patients were available for this analysis. Cumulative Kaplan-Meier incidence estimates for DQA1*0102 carriers and non-carriers treated with lumiracoxib were compared to the estimates for ibuprofen, naproxen, and the lumiracoxib arm as a whole. In this European patient population, the DQA1*0102 non-carriers had ALT/AST elevation incidences below ibuprofen-treated patients. In the European region (including South Africa), all 28 lumiracoxib-treated patients with >5xULN elevations were carriers for the DQA1*0102 allele. However, the frequency of DQA1*0102 may vary among the European populations. The Applicant should comment on any impact of possible interethnic differences (including differences among European populations) on the predictive values of DQA1*0102 genotype. The Applicant should also provide country specific data (in tabulation) regarding the performance of the DQA1*0102 marker. The genetic data in other ethnic populations are at present not available. The Applicant is asked to comment on the advice to be given regarding lumiracoxib treatment and genotyping in patients of other ethnicity than Caucasians.

Identification of additional markers

The genome-wide analysis was repeated using all patients (134 cases of >3x ULN AST/ALT and 566 controls) who had been included in the case/control analyses in order to identify any additional SNPs that failed to achieve study-wide significance in the original smaller genome-wide screen. Principal components analysis (PCA) was used in the genome-wide screens to avoid confounding by ancestry and to more accurately classify patients for ancestry-specific analysis. Analyses controlled for DQA1*0102 carrier status, study (0117 or 2332) and ancestry.

These analyses failed to clearly identify a second independent marker associated with lumiracoxib-related hepatotoxicity. However, it is likely that this study is not adequately powered to detect the effect of genetic markers with small effect sizes.

SNP rs3131294, shown to have the most significant association (p=4.0x10-21) to lumiracoxib-related hepatotoxicity, failed the quality control cut-off for missing genotype data (4.1% missing) in the initial genome-wide screen. This SNP is located in NOTCH4 and is in the MHC class III region adjacent to the MHC class II region. Analysis was performed using rs3131294 with DQA1*0102 in a two-marker model but this did not substantively improve the predictive parameters. The Applicant has performed further analysis of the NOTCH4 gene region in addition to the larger MHC region. Current evidence still supports the view that functionally relevant polymorphisms most likely reside in the classic HLA genes and not in C6orf10 or NOTCH4.

An attempt was made to identify a combination of two or more genetic markers that, taken together as a multi-marker model, could attain higher levels of sensitivity and NPV than the DQA1*0102 allele alone. Since no markers outside the HLA region reached genome-wide significance in any genome-wide analyses performed, this multi-marker analysis was restricted to markers in the HLA region. The

two-marker model, in patient carrying at least one copy of either or both of the DRB1 alleles (DRB1*1501 and DRB1*1302), yielded a slightly higher NPV than the DQA1*0102 allele alone (99.06% compared to 99.03%). However, this difference is considered too small to be distinguishable from random chance.

Additional cases of Hy's Law and > 5x ULN ALT/AST are currently being collected from Study 2483 (see below). The genome-wide data from these additional cases will be combined with the previous TARGET dataset of >3x ULN ALT/AST cases (n=134) and controls (n=566) for a new genome-wide analysis, to increase the statistical power for identifying other markers associated with lumiracoxib-related hepatotoxicity.

DQA1*0102 marker analysis by ancestral group

The case-control study comprised 85% Caucasians and 14% Hispanics. Principal component analysis was used to more accurately define ancestral group, leading to the re-classification of several Caucasians as Hispanic. Since genome-wide data is required to generate the principal components, this analysis was restricted to the 700 patients included in the exploratory genome-wide analysis. While the results of the analysis show that screening patients based on DQA1*0102 carrier status would reduce the risk of liver toxicity in the Hispanic-PC cluster, this biomarker does not perform as well in the Hispanic-PC cluster as in the Caucasian-PC cluster. It is of major concern that the biomarker does not appear to perform as well in Hispanics. There is no data to allow an estimation of the predictive parameters in other ethnic groups that might be relevant in a European population.

**Sensitivity and number of cases with the DQA1*0102 allele as a function of severity of liver enzyme (ALT/AST elevations) and principal components defined ancestral groups**

| | All Races | | Caucasian-PC | | Hispanic-PC | |
|---|---|---|---|---|---|---|
| ALT/AST Threshold | Sensitivity | Carriers/ cases | Sensitivity | Carriers/ cases | Sensitivity | Carriers/ cases |
| >3xULN | 74.6% | 100/134 | 82.9% | 87/105 | 42.3% | 11/26 |
| >5xULN | 83.6% | 51/61 | 91.7% | 44/48 | 58.3% | 7/12 |
| >8xULN | 90.9% | 30/33 | 100.0% | 25/25 | 71.4% | 5/7 |
| >10xULN | 91.7% | 22/24 | 100.0% | 19/19 | 60.0% | 3/5 |
| >15xULN | 93.8% | 15/16 | 100.0% | 12/12 | 75.0% | 3/4 |
| >20xULN | 100.0% | 8/8 | 100.0% | 6/6 | 100.0% | 2/2 |

The Applicant has provided sensitivity and NPV, including confidence intervals for the >3x and > 5x rises in the PC defined ancestral groups, as shown in Table 2-11:

**Table 2-11 Sensitivity, NPV and presence of DQA1*0102 allele in PC defined ancestral groups by ALT/AST elevation**

| | All Races | | | Caucasian-PC | | | Hispanic-PC | | |
|---|---|---|---|---|---|---|---|---|---|
| ALT/ AST rise | Carriers /cases | Sensitiv.[a] (95% CI) | NPV[b] (95% CI) | Carriers /cases | Sensitiv. (95% CI) | NPV (95% CI) | Carriers/ cases | Sensitiv. (95% CI) | NPV (95% CI) |
| **>3x** | 100/134 | **74.6%** (66.4,81.7) | 99.06% (98.7,99.3) | 87/105 | **82.9%** (74.3,89.5) | 99.33% (99.00,99.6) | 11/26 | **42.3%** (23.4,63.1) | 98.06% (97.3,98.6) |
| **>5x** | 51/61 | **83.6%** (71.9,91.8) | 99.71% (99.5,99.8) | 44/48 | **91.7%** (80.0,97.7) | 99.84% (99.68,99.9) | 7/12 | **58.3%** (27.7,84.8) | 99.45% (98.9,99.7) |

NPV = negative predictive value, Sensitiv. = sensitivity, CI = confidence interval, PC = principal components
[a] CIs based on exact binomial method, [b] CIs based on (Mercaldo, Lau and Zhou 2007) method for samples enriched for cases
Source: New analysis

The negative predictive value for the Hispanic-PC group could be as low as 97.3% based on the 95% confidence interval. Thus the percentage of non-carriers who might experience elevated liver enzymes >3xULN could be as high as 2.7%. This could be considered a worst case scenario, but is relevant for drug with a known serious safety issue.

The Applicant has proposed a 2-factor model (excluding patients with DQA1*0102 and/or >1x ULN ALT/AST) as a strategy to further reduce the risk of hepatotoxicity in non-Caucasians, as illustrated for Hispanics in Table 2-9 below. However, this model does not appear to reduce risk at the 100mg daily dose level (see Table 1-19 above).

**Table 2-9 Predictive parameters in the 2-factor[a] model with DQA1*0102 as the single predictor in lumiracoxib-treated Hispanic-PC patients**

| | Sensitivity | | PPV | | NPV | |
|---|---|---|---|---|---|---|
| **ALT/AST elevation** | 2-factor model | DQA1*0102 alone | 2-factor model | DQA1*0102 alone | 2-factor model | DQA1*0102 alone |
| >20xULN | 100.0% (2/2) | 100.0% (2/2) | 0.6% | 0.7% | 100.00% | 100.00% |
| >15xULN | 100.0% (4/4) | 75.0% (3/4) | 1.2% | 1.0% | 100.00% | 99.91% |
| >10xULN | 80.0% (4/5) | 60.0% (3/5) | 1.7% | 1.4% | 99.87% | 99.76% |
| >8xULN | 85.7% (6/7) | 71.4% (5/7) | 2.3% | 2.1% | 99.88% | 99.78% |
| >5xULN | 83.3% (10/12) | 58.3% (7/12) | 3.7% | 2.8% | 99.78% | 99.45% |
| >3xULN | 57.7% (15/26) | 42.3% (11/26) | 6.4% | 5.2% | 98.54% | 98.06% |

[a]The 2-factor predictive model assumes that patients who carry the DQA1*0102 allele and/or have ALT and AST >1xULN at screening would be excluded from treatment with lumiracoxib
Source: New analysis

Comparison of DQA1*0102 carriers and non-carriers for overall safety

To evaluate whether efficacy and safety (aside from hepatotoxicity) in the DQA1*0102 non-carrier population is similar to that observed in the DQA1*0102 carrier population, an analysis was performed

on the TARGET genetic sub-study. All 4518 lumiracoxib-treated patients that were successfully genotyped for the DQA1*0102 allele were included in this analysis.

The incidence of common adverse events (≥3% incidence among carriers, non-carriers, or both), regardless of study drug relationship, were compared between DQA1*0102 carriers and non-carriers by primary system organ class for lumiracoxib-treated patients. The results show that all adverse event incidences are similar between DQA1*0102 carriers and non-carriers, with the exceptions of (1) hepatobiliary disorders, as would be expected, and (2) investigations, which include ALT and AST elevations. The system organ class Immune system disorders is not included in the table below. However the Applicant has provided data to show that the incidence of AEs from this SOC is similar in carriers and non-carriers.

**Comparison of incidence of common adverse events, by primary system organ class, between DQA1*0102 carriers and non-carriers in lumiracoxib-treated patients**

| Primary system organ class | DQA1*0102 carriers (n=1518) | DQA1*non-carriers (n=3000) |
|---|---|---|
| | n (%) | n (%) |
| Cardiac disorders | 61 (4.0%) | 127 (4.2%) |
| Ear and labyrinth disorders | 54 (3.6%) | 99 (3.3%) |
| Gastrointestinal disorders | 769 (50.7%) | 1535 (51.2%) |
| General disorders and administration site conditions | 154 (10.1%) | 351 (11.7%) |
| Hepatobiliary disorders | 50 (3.3%) | 43 (1.4%) |
| Infections and infestations | 506 (33.3%) | 978 (32.6%) |
| Injury, poisoning, and procedural complications | 141 (9.3%) | 276 (9.2%) |
| Investigations | 177 (11.7%) | 228 (7.6%) |
| Metabolism and nutrition disorders | 57 (3.8%) | 135 (4.5%) |
| Musculoskeletal and connective tissue disorders | 397 (26.2%) | 789 (26.3%) |
| Nervous system disorders | 310 (20.4%) | 620 (20.7%) |
| Psychiatric disorders | 74 (4.9%) | 166 (5.5%) |
| Renal and urinary disorders | 55 (3.6%) | 100 (3.3%) |
| Respiratory, thoracic, and mediastinal disorders | 116 (7.6%) | 253 (8.4%) |
| Skin and subcutaneous tissue disorders | 125 (8.2%) | 221 (7.4%) |
| Vascular disorders | 109 (7.2%) | 270 (9.0%) |

The incidence of key adverse events for GI (definite/probable UGIT ulcer complications), CV (APTC endpoint), and major renal events were compared between DQA1*0102 carriers and non-carriers. No significant differences were observed between the DQA1*0102 carriers and non-carriers.

**Incidence of key AEs in TARGET by DQA1*0102 carrier status**

| AE | Carrier (n=1518) | Non-carrier (n=3000) |
|---|---|---|
| Definite/probable UGIT[1] ulcer complications | 5 (0.33%) | 8 (0.27%) |
| APTC[2] endpoint | 8 (0.53%) | 19 (0.63%) |
| Major renal events[3] | 8 (0.53%) | 9 (0.30%) |

[1]UGIT= upper gastrointestinal tract
[2]APTC= antiplatelet trialists' collaboration (includes MI, stroke, and cardiovascular death)
[3]A major renal event was defined as one in which serum creatinine increased by ≥100% from baseline and/or urine protein was ≥3.0 g/L (by urine dipstick)

Comparison of genotyped and non-genotyped patients

A comparison was made between DQA1*0102 genotyped and non-genotyped lumiracoxib-treated patients to assess whether the genotyped patients were representative of the full TARGET lumiracoxib population. These two patient groups were compared on the basis of incidence of elevated liver enzymes, incidence of non-hepatic adverse events, and efficacy.

The incidence of elevated liver enzymes and the most common non-hepatic adverse events was higher among genotyped patients than among non-genotyped patients. The same trend was observed among ibuprofen-treated patients and among naproxen-treated patients. It was discussed that the higher incidence of elevated liver enzymes among genotyped patients may be due to better compliance in patients who consented to provide DNA (more likely to appear for all scheduled visits and to provide all the necessary laboratory samples) and in an investigator/centre (more likely to attempt to obtain a DNA sample and to ensure that all required laboratory measures are taken). In either case, the more laboratory measures that are taken, the greater the chance of observing an ALT/AST elevation that may have been missed otherwise. There was a general trend for the genotyped population to show improved efficacy compared to non-genotyped. This was observed in all treatment arms.

The subpopulation chosen for genotyping does not appear to be representative for the overall population of patients included in the TARGET study. These differences raise concerns whether the results obtained for the DQA1*0102 genotyped TARGET subpopulation can be extrapolated to the general population intended to be treated with lumiracoxib in daily practice. Consent was obtained prospectively, as confirmed in the TARGET protocols. The Applicant has carried out several new analyses in an attempt to explain the discrepancies. It does appear that the number of liver enzyme measurements is a confounder. This finding is supportive of the Applicant's view that the imbalance is likely to be a combination of patient and physician effects. It is accepted, based on the Applicant's analysis of drop-outs, that the difference in rates of elevated transaminases is unlikely to be affected by patients dropping out before DNA sampling could take place. The reason for the imbalance is not known. However it is unlikely to be the result of bias. The extrapolation of the predictive parameters of the DQA1*0102 from genotyped patients to the overall TARGET population is considered acceptable.

Study 2483

Following the Day 120 CHMP LoQ, the Applicant is further validating the findings of the pharmacogenetic study in an independent set of patients with the most notable hepatic AEs (Hy's law cases or AST/ALT >10x ULN) from earlier lumiracoxib trials in a new study.

Study 2483 is an ongoing retrospective post-hoc pharmacogenetic study of patients with elevated liver enzymes (in previously run studies, whose data could not be included in the TARGET pharmacogenetic analysis). The goal is to contact and obtain consent for genetic testing in these patients and determine their DQA1*0102 allele status. The core study 2483 includes patients with Hy's law cases or AST/ALT > 10x ULN. Of the 37 patients targeted for participation in this core study (8 who met Hy's law criteria and 29 patients with aminotransferases >10x ULN), 19 patients are still contactable (4 of the 8 Hy's law patients and 15 of the 29 >10x ULN AST and/or ALT patients).

*Hy's Law cases:*

4 patients have been contacted, of which 3 have been tested. 3 out of 3 are carriers of DQA1*0102, one of which is Chinese. One Hy's Law case has been found to have Gilbert's (homozygous for the UGT1A1*28 allele). Of the 6 Hy's Law cases now genotyped (3 from the original pharmacogenetic sub-

study, 3 from study 2483), all 6 are carriers of DQA1*0102. Of these, 2 are non-caucasian (one Chinese, one 'other' from South Africa).

**Table-1 Hy's law cases in the entire clinical database (TARGET and patients from study 2483)**

| | Country | Race (self-reported) | DQA1*0102 carrier |
|---|---|---|---|
| Patient 1 [b] | NLD | Caucasian | Yes |
| Patient 2 [a] | USA | Caucasian | Yes |
| Patient 3 [a] | UK | Caucasian | Yes |
| Patient 4 [b] | CAN | Caucasian | Yes (Gilbert's syndrome) |
| Patient 5 [a] | ZAF | Other | Yes |
| Patient 6 [b] | CHN | Asian | Yes |
| Patient 7 [b] | COL | Hispanic | Sample being sought |
| Patient 8 [b] | TWN | Asian | Patient deceased |
| Patient 9 [b] | CHN | Asian | Patient deceased |
| Patient 10 [b] | CZE | Caucasian | Patient deceased |
| Patient 11 [b] | DEU | Caucasian | Patient not contactable |

[a] Patient from original TARGET pharmacogenetic sub-study

[b] Patient from 2483 core study

Source: TARGET pharmacogenetic sub-study [COX189A 0117-2332ad1], data from ongoing study A2483

*>10x ALT/AST*

The Applicant states that 11 out of 13 cases of >10x ULN ALT/AST in Study 2483 were carriers of DQA1*0102. However, from the data provided, there appear to be 10 cases, all Caucasian, of which 8 were carriers. This gives a sensitivity of 80%, which is lower than the 92.0% reported in the TARGET pharmacogenetic sub-study. The Applicant should clarify.

Information is provided for the patients in Core Study 2483 who were not contactable. Reasons included death, site closed by HA, lost to follow-up, unable to consent, unwilling to consent, investigator not responding.

The study has been extended to include patients with >5x but ≤ 10x ULN ALT/AST. Some data may be available at Day 180.

Discussion of pharmacogenetic study

The methods used to identify genetic markers associated with an increased risk of developing elevated liver enzymes after treatment with lumiracoxib are considered acceptable The associations between the identified SNPs in MHC class II region, and lumiracoxib-related transaminase rises are highly statistically significant. The replication of the findings in an independent case-control set also provides good evidence of association. HLA genotyping and analysis of all cases (n=137) and controls (n=577) identified a strong association to a well characterized HLA haplotype (DRB1*1501-DQB1*0602-DRB5*0101-DQA1*0102).The choice of DQA1*0102, from among the alleles identified, as the marker with the best performance characteristics is supported.

While the negative predictive values for the DQA1*0102 are impressive, it appears from the data that the crude rates and estimated risk of a rise in transaminase for non-carriers on lumiracoxib remain elevated compared to naproxen or ibuprofen, particularly at the >3x ULN level. Furthermore as hepatotoxicity is a serious safety issue it is important to consider the lower limit of the confidence interval as well as the point estimate of the predictive parameters. However, the performance of the DQA1*0102 marker improves as the severity of transaminase rise increases. There were 9 Hy's law cases in the lumiracoxib arm, of which 6 have been genotyped and all found to be carriers of DQA1*0102. The Applicant proposes a 2-factor model (exclusion of DQA1*0102 and >1x ULN ALT/AST) to further reduce the risk of hepatotoxicity, based on a new analysis to identify independent non-genetic risk factors. However this model adds further complexity to the L-RAP, yet does not appear to reduce risk at the 100mg daily dose level.

There are no data comparing lumiracoxib 400 mg treated DQA1*0102 non-carriers with celecoxib or NSAIDs other than ibuprofen and naproxen. There are no data on the clinical utility of DQA1*0102 genotyping in patients treated with 100mg dose. A post-authorisation Registry study using historical controls has been planned to address the performance of DQA1*0102 marker in patients taking 100mg dose.

The DQA1*0102 biomarker appears to perform less well in the largest non-Caucasian group studied, the Hispanics, when compared to Caucasians, based on the available data. There is little data on other ethnic groups. It is not known whether genetic differences between different ethnic groups, such as allele frequency, would affect the performance of the biomarker. The justification for extrapolation of the indication to non-Caucasian ethnic groups, based on the introduction of a 2-factor model, is not considered supported by the data.

## Discussion on clinical safety

The safety profile of NSAIDs, including COX-2 inhibitors is well recognized. Gastrointestinal, cardiovascular and renal adverse effects, hypersensitivity or skin reactions and hepatotoxicity are known class effects. With regard to lumiracoxib the safety database is extensive. More than 40 000 patients have been exposed to lumiracoxib in clinical trials.

The overall safety of lumiracoxib, as described by AEs, SAEs, deaths and discontinuations, is similar to comparators, including celecoxib, ibuprofen and naproxen.

Upper gastrointestinal safety, including risk of perforations, ulcers, bleeding and symptomatic ulcers (PUBs) is similar to celecoxib and superior to traditional NSAIDs (including ibuprofen, naproxen). The lower complication rates for the 400mg od regimen, compared to the NSAIDs naproxen and ibuprofen, as demonstrated in TARGET are clinically important. However, the reduced risk has not been demonstrated in low dose aspirin users. Data suggests that lumiracoxib related GI AEs and complications are dose-dependent. Therefore 100mg daily is expected to show a favourable profile compared to traditional NSAIDs.

There is no evidence of an increased pro-thrombotic risk compared to celecoxib. Data from TARGET at the 400mg dose suggest that lumiracoxib is associated with a small increase in thrombotic events (especially myocardial infarction) in comparison to naproxen (particularly in non-aspirin users) when treatment is limited to 1 year. This study does not provide any evidence of increased risk of thrombotic events for lumiracoxib versus ibuprofen. CHMP have previously provided an opinion that there is an increased cardiovascular risk with COX-2 inhibitors, and there is an association with dose and duration of use. Therefore 100mg daily is expected to be associated with a reduced risk compared to 400mg daily, as studied in TARGET.

Lumiracoxib appears to have an improved blood pressure safety profile compared to ibuprofen, supported by data from Study 2428. However it should be noted that this study did not contain a placebo arm. Therefore it is not possible to conclude that lumiracoxib lowers blood pressure.

There is some evidence of a less favourable renal profile relative to comparators. There is an increased rate of adverse biochemical changes, but not an increased risk of renal SAEs. A contraindication in moderate/severe renal impairment is proposed.

Hepatotoxicity

In the longer term databases, an increased rate of transaminase elevation >3x ULN is clearly seen, even for the 100mg dose. No Hy's Law cases have been reported in the clinical trials at 100mg daily. However there were 7 cases of >5x ULN AST/ALT. Since marketing, spontaneous reports have been received for 10 severe hepatic cases at 100mg daily, including 1 death and 1 transplant.

Following revocation of marketing authorisations in Europe in 2008, as a result of hepatotoxicity, the Applicant has submitted the results of a pharmacogenetic sub-study of TARGET. The selection of the DQA1*0102 biomarker for identification of patients at greater risk of hepatotoxicity is considered acceptable. However, concern remains regarding the excess of cases of >3x ULN ALT/AST with 400mg daily in non-carriers from TARGET, relative to ibuprofen and naproxen. From the available data, it is not possible to quantify the expected risk reduction following use of the biomarker at the 100mg daily dose level. The Applicant is collecting genetic data from all >5x ULN ALT/AST cases in the clinical database. These data may provide additional validation and reassurance.

The DQA1*0102 biomarker appears to perform less well in the largest non-Caucasian group studied, the Hispanics, when compared to Caucasians, based on the available data. There is little data on other ethnic groups. It is not known whether genetic differences between different ethnic groups, such as allele frequency, would affect the performance of the biomarker. The justification for extrapolation of the indication to non-Caucasian ethnic groups, based on the introduction of a 2-factor model, is not considered supported by the data.

## Conclusions on clinical safety

The clinical safety profile of lumiracoxib 100mg od was assessed in detail at the time of the Article 107 referral in November 2007, which led to the revocation of marketing authorisations across the EU on the grounds of hepatotoxicity. Aside from hepatotoxicity, the safety conclusions are essentially unchanged. The GI safety profile is comparable to celecoxib and superior to traditional NSAIDs. The Cardiovascular profile is in line with known COX-2 class effects. The renal profile appears slightly inferior to celecoxib biochemically. The blood pressure profile appears to be superior to ibuprofen.

It appears from the pharmacogenetic data that the use of the DQA1*0102 allele would reduce the risk of lumiracoxib-related hepatotoxicity. However major outstanding issues remain (see Section 5).

## Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

## Risk Management plan

### *Safety Specification*

Based on the safety specification the applicant lists the following as ongoing safety concerns:

**Table 1-45 Ongoing safety concerns**

| | |
|---|---|
| Important identified risks | Hepatic disorders |
| | Gastrointestinal disorders |
| | Cardiac and cerebrovascular disorders |
| | Renal disorders |
| | Hypersensitivity reactions |
| Important potential risks | SCARs |
| Important missing information | Patients below 18 years |
| | Pregnancy |

### *Pharmacovigilance Plan*

The applicant proposes routine pharmacovigilance activities for all important identified risks, potential risks and missing information with the exception of the identified risk of hepatic disorders, where the applicant plans to conduct a post-approval safety study with independent adjudication of abnormal liver function tests (Hy's law cases), liver failure, liver transplant or death.

The applicant lists the following planned actions in the pharmacovigilance plan;

**Table 2-1 Safety concerns and planned pharmacovigilance actions**

| Safety Concern | Planned action(s) |
|---|---|
| Important identified risks | |
| Hepatic disorders | Routine pharmacovigilance including cumulative analysis in PSUR. For listed events foccus on increased severity and frequency and higher specificity. |
| | PASS Registry CCOX189A2482 incl. adjudication of all potential Hy's law cases and hepatic events of special interest (hepatic failure, liver transplant, death) by an independent LSC. |
| Gastrointestinal disorders | Routine pharmacovigilance including cumulative analysis in PSUR. For listed events foccus on increased severity and frequency and higher specificity. For listed events foccus on increased severity and frequency and higher specificity. |
| Cardiac and cerebrovascular disorders | Routine pharmacovigilance including cumulative analysis in PSUR. For listed events foccus on increased severity and frequency and higher specificity. |
| Renal disorders | Routine pharmacovigilance including cumulative analysis in PSUR. For listed events foccus on increased severity and frequency and higher specificity. |
| Hypersensitivity reactions | Routine pharmacovigilance including cumulative analysis in PSUR. For listed events foccus on increased severity and frequency and higher specificity. |
| Important potential risk | |

| Safety Concern | Planned action(s) |
|---|---|
| Important identified risks | |
| SCARs | Routine pharmacovigilance including cumulative analysis in PSUR. |
| Important missing information | |
| Patients below 18 years | Routine pharmacovigilance including cumulative analysis in PSUR. |
| Pregnancy | Routine pharmacovigilance including cumulative review in PSUR |

## *Evaluation of the need for a Risk Minimisation plan*

The applicant justified the need for risk minimisation activities;

| Safety concern | Routine risk minimization activities sufficient? | If yes, provide description of routine activity and justification |
|---|---|---|
| | | CDS Section 6 (Warnings and precautions) and 9 (Pregnancy and breast-feeding). |
| | | SPC section 4.2 (Posology and method of administration) 4.3 (Contraindications), 4.4 (Special warnings and precautions for use) and 4.6 (Pregnancy and lactation) |

### *Risk Minimisation plan*

The applicant proposes several risk minimisation activities to minimise the risk of hepatic disorders.

The risk management plan for lumiracoxib is not considered acceptable at present and further amendment and clarification is required. A detailed assessment of the applicant's revised RMP has led to several outstanding issues.

# ORPHAN MEDICINAL PRODUCTS

N/A

# BENEFIT RISK ASSESSMENT

## Benefits

## Beneficial effects

The efficacy data is considered supportive of the claimed indication **Symptomatic relief in the treatment of osteoarthritis of the knee and hip in patients who are non-carriers of the DQA1*0102 allele**. The pivotal trials were well-designed and well-conducted. The study populations were appropriate. Lumiracoxib 100 mg daily has been shown to be consistently superior to placebo, in providing symptomatic relief, in patients with knee and hip OA. The effect sizes, although relatively small, are consistent across the pivotal hip and knee studies, and are comparable to celecoxib 200mg daily. Clinical relevance is therefore concluded. Efficacy data from other clinical studies conducted at higher doses and/or different indications is considered supportive of efficacy at the claimed dose and indication.

The applicant has provided an analysis of efficacy in non-carriers of DQA1*0102, albeit at the 400mg dose. This supports the efficacy conclusions for the restricted indication population of non-carriers.

Lumiracoxib, like all NSAIDs, is associated with gastrointestinal toxicity. However, in line with other COX-2 inhibitors, the GI profile is favourable compared to non-selective NSAIDs. This conclusion is supported by data from TARGET, at the 400mg dose, when compared to ibuprofen 800mg tid and naproxen 500mg bd. The benefit was greatest in non-aspirin users. Due to dose-dependent toxicity, lumiracoxib 100mg daily is expected to show an improved GI safety profile compared to 400mg od.

Lumiracoxib does not contain a sulfonamide or sulfone moity and is not contra-indicated in patients with sulfonamide drug allergies, which provides some clinical benefit for patients with sulfonamide drug allergies.

Based on the clinical safety database, lumiracoxib appears to produce smaller increase in blood pressure with less aggravation of existing hypertension and less de novo hypertension as compared with traditional NSAIDs. A confirmatory study (2428) in OA patients with controlled hypertension showed a statistically and clinically significant reduction in mean ambulatory blood pressure after 4 weeks on lumiracoxib 100mg daily compared to ibuprofen 600mg tid. However as there was no placebo arm, it is not possible to conclude that lumiracoxib lowers blood pressure.

## Uncertainty in the knowledge about the beneficial effects

None.

## Risks

## Unfavourable effects

Clinical trial and post-marketing data clearly demonstrate that lumiracoxib has a worse hepatic safety profile than comparators, including celecoxib, ibuprofen,and naproxen, when used in a general OA hip and knee population at 100mg daily. For this reason, EU marketing authorisations were revoked in 2008.

Overall, the risks of lumiracoxib, other than hepatotoxicity, are considered to be in line with the known class effects of NSAIDs in general and COX-2 inhibitors in particular. The safety conclusions are consistent with those of previous European procedures concerning lumiracoxib. The extensive database submitted with this application does not raise any new safety concerns.

As compared to naproxen, observed in TARGET, lumiracoxib is associated with a small increase in thrombotic events, especially myocardial infarction (particularly in non-aspirin users).

There is some evidence of a less favourable renal profile relative to comparators, in the form of increased rates of adverse biochemical changes. However this does not translate to an increased risk of renal SAEs in clinical trials. Postmarketing reports of renal disorders are considered to be consistent with the known class effect.

## Uncertainty in the knowledge about the unfavourable effects

The Applicant has conducted a separate retrospective validation study (2483), which provides some l reassurance that use of the DQA1*0102 biomarker would reduce lumiracoxib-related hepatotoxicity. However, concern remains regarding the excess of cases of >3x ULN ALT/AST with 400mg daily in non-carriers from TARGET, relative to ibuprofen and naproxen. From the available data, it is not possible to quantify the expected risk reduction following use of the biomarker at the 100mg daily dose level. The Applicant is collecting genetic data from all >5x ULN ALT/AST cases in the clinical database. These data may provide additional validation and reassurance.

The DQA1*0102 biomarker appears to perform less well in the largest non-Caucasian group studied, the Hispanics, when compared to Caucasians, based on the available data. There is little data on other ethnic groups. It is not known whether genetic differences between different ethnic groups, such as allele frequency, would affect the performance of the biomarker. The justification for extrapolation of the indication to non-Caucasian ethnic groups, based on the introduction of a 2-factor model (DQA1*0102 carrier status and >1x ULN ALT/AST) is not considered supported by the data.

An acceptable hepatic safety profile also relies upon the effectiveness of the Risk Management Plan, which includes the lumiracoxib restricted access program (L-RAP). The Applicant has tried to simplify the L-RAP program with less involvement of pharmacists, allowing for flexibility within the member states. Although these proposals may be considered an improvement, the L-RAP is still considered complicated, and would place significant burden on the healthcare system, particularly patients. The Applicant has not provided re-assurance that the L-RAP is workable in all member states.

## Balance

## Importance of favourable and unfavourable effects

Osteoarthritis of the hip and knee is a common condition which while disabling is benign. It is treated mainly in primary care. There are a range of alternative treatments which are as effective as lumiracoxib. In this context, it is considered that any increased risk of hepatotoxicity in the DQA1*0102 non-carrier population, relative to comparators, is of great importance.

## Benefit-risk balance

Efficacy in the claimed indication, and a favourable GI safety profile compared to non-selective NSAIDs is concluded. The non-hepatic risks appear comparable to other NSAIDs, in line with the previous opinions of CHMP. However the benefits are outweighed by the remaining uncertainty concerning the residual risk of hepatotoxicity in DQA1*0102 non-carriers (particularly in non-Caucasians), and the utility, practicality and burden to patients of the restricted access program.

## Conclusions

The overall B/R of Joicela 100 mg film-coated tablets is negative.