21 February 2013
EMA/393189/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nevanac

International non-proprietary name: NEPAFENAC

Procedure No. EMEA/H/C/000818/X/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Quality

API: Active Pharmaceutical Ingredient

IR: Infrared spectroscopy

HPLC: High performance liquid chromatography

IPC: In-process control

KF: Karl Fisher titration

LOD: Limit of detection

LOQ: Limit of quantification

ND: Not detected

NMT: Not more than

Non-Clinical

BLQ: below the limit of quantitation

CMC: carboxymethyl cellulose

DMSO: dimethyl sulfoxyde

ECG: electrocardiogram

HPLC: high performance liquid chromatography

ICB: iris-ciliary body

LSC: liquid scintillation counting

MS: mass spectrometry

NSAID: non-steroidal anti-inflammatory drug

PGE_2: prostaglandin E_2 (dinoprostone)

QD: once a day

TID: three times a day

UPLC: ultra performance liquid chromatography

VEGF: vascular endothelial growth factor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Alcon Laboratories (UK) Ltd submitted on 4 May 2012 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Nevanac, 3mg/ml, eye drop suspension, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indent a, c) of the Commission Regulation (EC) No 1234/2008 .

Alcon Laboratories (UK) Ltd is already the Marketing Authorisation Holder for Nevanac, 1 mg/ml, eye drops, suspension (EU/1/07/433/001).

The applicant applied for the following indication: Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/16/2011 on the granting of a product-specific waiver.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 December 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Nevanac 1 mg/ml has been given a Marketing Authorisation in European Countries on 11 December 2007.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 4 May 2012.
- The procedure started on 23 May 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2012
- During the meeting on 17-20 September 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2012

- The applicant submitted the responses to the CHMP consolidated List of Questions on 9 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 January 2013
- During the CHMP meeting on 14-20 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 January 2013.
- During the meeting on 18- 21 February 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nevanac 3 mg/ml.

2. Scientific discussion

2.1. Introduction

Inflammation following cataract surgery is a normal physiological response to trauma and typically resolves in time without intervention. However, within the eye, the effects of inflammation can result in detrimental conditions. Mild to moderate ocular inflammation may be associated with discomfort (mild to moderate ocular pain and/or photophobia), while more severe inflammation may be associated with more significant complications including decreased vision, severe pain/photophobia, formation of posterior synechiae, elevated intraocular pressure, worsening of pre-existing glaucoma, deposits on the intraocular lens, vitreous haze and/or cystoid macular oedema.

The inflammatory reaction is believed to be mediated by prostaglandins released in the anterior segment. Anti-inflammatory therapies are administered to reduce postoperative inflammation and to help prevent the posterior segment complication of cystoid macular oedema. While corticosteroids are very effective in controlling inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as well and, when used preoperatively, may also inhibit the development of inflammation. Numerous NSAIDs are approved currently in EU Member States and include diclofenac sodium 1 mg/ml, ketorolac trometamol 5 mg/ml, bromfenac sodium 1 mg/ml and Indomethacin 1 mg/ml.

Nepafenac belongs to the class of NSAIDs. It is a prodrug (amfenac amide) which is converted to amfenac by intraocular hydrolases. Amfenac inhibits both cyclooxygenase COX-1 and COX-2 activity.

Nepafenac at a concentration of 1 mg/ml (0.1%) has been authorised in December 2007 under the trade name Nevanac for marketing in the EU through the centralised procedure for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery. Nevanac is also indicated for reducing the risk of developing macular oedema following cataract surgery in diabetic patients. When used in the indication of postoperative pain and inflammation Nevanac should be applied up to 21 days of the postoperative period; for prevention of macular oedema, Nevanac should be used up to 60 days after surgery.

The dosing regimen of nepafenac 1 mg/ml in the approved indications is three times daily. With this application, Alcon proposed the introduction of a new formulation of nepafenac, in which the concentration of nepafenac has been increased from 1 mg/ml (0.1%) to 3 mg/ml (0.3%) to be

administered once daily. Additionally the particle size of nepafenac has been reduced and the vehicle has been modified with the addition of a carbopol-guar to increase viscosity of the suspension, thereby enhancing ocular retention and bioavailability. The new formulation is proposed to be used for prevention and treatment of postoperative pain and inflammation associated with cataract surgery.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as eye drops, suspension, containing 3 mg/ml of nepafenac as the active substance. The full qualitative composition is described in section 6.1. of the SmPC.

The product is available in LDPE bottle with a dispensing plug and polypropylene screw cap, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance is the same as for the already authorised strength 1 mg/ml. Current ASMF, which was also submitted with this line extension application, was approved by a type II variation II/0001 in September 2008.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective was to develop a new strength of the same pharmaceutical form which can be administered once daily compared to already authorised 1 mg/ml strength which has to be administrated 3 times a day. This was achieved by increasing the active substance concentration, ocular retention time and reducing the particle size of nepafenac, which resulted in increased drug ocular bioavailability. These modifications were predicted to increase target tissue drug levels and achieve efficacy similar to nepafenac 1mg/ml dosed 3 times daily.

The concentration of nepafenac was increased from 1 mg/ml to 3 mg/ml. The formulation design of the 3 mg/ml concentration is based on the approved product of 1 mg/ml. To enhance ocular retention, the vehicle was modified with the addition of a compendial biopolymer (guar). The particle size of nepafenac in this new formulation was reduced to roughly one-third the particle size of nepafenac in nepafenac 1 mg/ml.

Since the active substance is practically insoluble in water, the product was developed as an isotonic aqueous suspension.

All excipients are compendial – benzalkonium chloride is used as antimicrobial preservative, carboxymethyl cellulose sodium as milling agent, guar as viscosity agent, carbomer 974P as viscosity agent, boric acid as viscosity modifying agent, disodium edetate as preservative aid, propylene glycol and sodium chloride are tonicity agents and sodium hydroxide and hydrochloric acid are used for pH adjustment, when needed.

Guar is considered a novel excipient, despite being listed in the Ph.Eur., as it is used in an ophthalmic medicinal product for the first time. Full information on this excipient was provided in the dossier. In

addition to tests required by the Ph.Eur., guar is tested for purity (phenolic compounds), residual solvents (ethanol), pesticide residues and pentachlorophenol.

In addition to guar, viscosity of the product is further optimised by carbopol and boric acid. Carbopol provides a structured suspension platform for the suspension, preventing settling and caking. The combination of guar and carbopol provides higher viscosity than carbopol alone. Boric acid interacts with guar; at 0.5% concentration it helps to maintain the target viscosity at pH of 6.8. The pH of 6.8 was selected in order to minimise formation of lactam, a degradant of nepafenac at lower pH. Higher pH would increase the viscosity of the solution, which would affect manufacturability of the product. The combination of carbopol, guar and boric acid also provides adequate buffering capacity at the target pH range and pH control during storage.

Carboxymethyl cellulose sodium (carmellose sodium) is used as a milling agent, which reduces particle aggregation and ensures consistent particle size in the suspension formulation. Its use for this purpose has been properly justified.

Benzalkonium chloride is used as an antimicrobial preservative because of a broad antimicrobial spectrum and because it is being widely used in topical ophthalmic preparations. The proposed concentration proves effective to meet Ph. Eur. “A” criteria for preservation. Edetate disodium is used as a preservative aid.

Terminal sterilization by heat was considered for the product but was not possible because of the heat sensitivity of the plastic bottle. Steam sterilization of the final bulk suspension was also considered. However, the active substance is heat-sensitive and consequently sterilization by gamma irradiation was chosen.

The applicant has evaluated three key characteristics (particle size, polymorphism and uniformity/homogeneity of dose) which could impact the quality of the suspension dosage form.
Particle size: The milling process applied in the manufacture of the product has been optimised to ensure uniform particle size in the suspension formulation, which has been appropriately tested. The particle size distribution data during the stability evaluation indicate that there are slight changes in the particle size distribution during long term storage.
Polymorphism of the drug substance and on the final formulation has been studied. The results from these studies strongly indicate that the formation of polymorphs in the suspension is not likely to occur.
Uniformity/homogeneity of dose: The product has been developed to be a homogeneous suspension which shows minimal sedimentation and is easily resuspendable. The resuspendability has been assessed on the primary stability batches and the product is resuspended within ten seconds. The homogeneity of the suspension between containers within a batch has been evaluated and showed uniform content of nepafenac. The homogeneity of the individual drops from a container was evaluated on stability samples of long term storage and showed that the patient is receiving a uniform dosage with every drop.

The primary packaging consists of round low density polyethylene bottle with a dispensing plug and white polypropylene screw cap containing 3 ml suspension. The packaging components have been previously approved for use in nepafenac 1 mg/ml eye drops and comply with the Ph.Eur.

Packaging compatibility studies were conducted for the eye drops and have demonstrated that there are no significant extractable or leachable impurities from the packaging components.

Adventitious agents

No materials derived from animal or human origin have been used.

Manufacture of the product

The same manufacturing process for the already authorised strength has been used and consists of the following steps: nepafenac milling, guar vehicle preparation/sterilization, carbomer/salt preparation and sterilization, and final compounding and filling.
All critical steps of the process, for example milling of the active substance, steps for the sterilisation of materials and equipment or the aseptic filling step, have been adequately studied and appropriate in process controls have been put in place to monitor them. Validation results demonstrate that the process is capable to reproducibly produce finished product of the intended quality.

Product specification

The finished product release specification includes tests appropriate for this kind of dosage form: appearance of suspension, identity (TLC, HPLC), assay (HPLC), impurities (HPLC), identity and assay of benzalkonium chloride (HPLC), identity and assay of sodium edetate (HPLC), pH (Ph.Eur.), osmolality (Ph.Eur.), redispersibility, viscosity (Ph.Eur.), particle size (light diffraction), fill volume and sterility (Ph.Eur.).

Degradation pathways of the active substance and the behaviour in the finished product have been extensively studied and are well documented. Three main degradation products were identified in the finished product. All specification limits correspond to relevant CHMP/ICH guidelines and Ph.Eur.

The testing methods are sufficiently described and all non-compendial methods are appropriately validated.

The batch analysis data of three primary stability batches show that the product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this ophthalmic preparation. Batch results of clinical and toxicology batches were provided as supportive data.

Stability of the product

Stability data of three primary stability batches and three supportive batches stored under long term conditions for up to 52 weeks at 25ºC/40%RH, up to 78 weeks at intermediate conditions at 30ºC/65%RH and 30ºC/75%RH (52 weeks), and for 26 weeks under accelerate conditions at 40ºC/25%RH according to ICH guidelines were provided.

In addition, the primary batches were exposed to light for 6 weeks.
The shelf-life specification includes the same tests as release specification, except all identity tests and fill volume. The limits of impurities are slightly higher than for release. The analytical procedures used were stability indicating.

A decrease in product viscosity was observed with time during storage. The viscosity decline is temperature dependent. Product exposure to extreme light also resulted in a change in viscosity, benzalkonium chloride and sodium edetate. According to the data available, other physicochemical parameters are not significantly affected by temperature or stress conditions.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Results of in-use stability testing of the finished product confirm the proposed in-use period.

2.2.4. 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 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

Results from additional non-clinical pharmacology, pharmacokinetic and toxicology studies were submitted in support of this application. In addition, reference was made to studies previously submitted at the time of the initial marketing authorisation application.

2.3.2. Pharmacology

Additional primary and secondary pharmacodynamic studies have been submitted by the MAH to support the marketing authorization of nepafenac 3 mg/ml, eye drops, suspension. Reference was also made to results from studies submitted with the initial marketing authorisation application.

Primary pharmacodynamic studies

The additional primary pharmacology studies performed included a series of in vitro studies examining the mechanism of action of nepafenac and a comparison with other NSAIDs, showing that nepafenac is not a time-dependent or slow-binding inhibitor of COX isoforms (COX-1 and COX-2).

An ex vivo prostaglandin E2 (PGE2) synthesis inhibition study in rabbits demonstrated that after topical single dose near-maximal inhibition remained 12 hours with 60% inhibition at 24 hours. This study was also performed with nepafenac 3 mg/ml formulations, with no significant differences when compared to Nevanac (i.e. nepafenac 1 mg/ml).

In addition, an in vivo study in anesthetised cats in order to measure the analgesic effects of nepafenac suggested that the product may act as an effective analgesic drug to rapidly reduce pain in the eye surface.

Secondary pharmacodynamic studies

Additional secondary pharmacology studies showed that nepafenac has a tendency to inhibit pre-retinal neovascularization in rat and mouse models of oxygen-induced retinopathy, and it showed an anti-angiogenic effect in the rat model.

In a diabetic retinopathy model in adult rats, the topical administration of nepafenac resulted in a reduction of the increment of several diabetes-induced markers, such as the increase in the number of apoptotic cells. Several of these studies were performed with 1 and 3 mg/ml concentrations, some also with 5mg/ml.

Safety pharmacology programme

The MAH did not conduct any additional safety pharmacology studies to support the application for nepafenac 3 mg/ml eye drops, suspension. The existing safety pharmacology studies did not show significant effects in the autonomic nervous, cardiovascular, pulmonary, gastrointestinal, metabolic and renal systems, and no significant interactions were evident in a battery of receptor binding assays with nepafenac.

Pharmacodynamic drug interactions

No pharmacodynamic interaction studies for nepafenac 3 mg/ml have been conducted by the MAH.

2.3.3. Pharmacokinetics

The results from three new ocular uptake and tissue distribution studies in New Zealand White Rabbits were presented by the MAH in order to support the application for nepafenac 3 mg/ml eye drops, suspension. For all three studies, the established methods of analysis demonstrated fully adequate accuracy, precision, specificity and stability for routine analysis of samples for both analytes.

Two studies were performed with single dose nepafenac ophthalmic suspension, one study using 3 mg/ml and the other 1 mg/ml formulations. The third study consisted of a comparison between nepafenac ophthalmic suspension 3 mg/ml (single dose) and Nevanac ophthalmic suspension 1 mg/ml [three times a day (TID)].

The exposure levels of nepafenac and amfenac, its active metabolite, were higher after a single dose of nepafenac ophthalmic suspension 3 mg/ml compared to those after the last TID dose of Nevanac ophthalmic suspension 1 mg/ml except for the lens, where the exposure levels were similar between the two treatment groups.

No additional absorption, metabolism, excretion and drug interaction studies were submitted in support of this application and reference was made to studies submitted previously with the initial marketing authorisation application.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were previously submitted. These studies showed a low potential for toxicity consistent with the NSAID class.

Repeat dose toxicity

Repeated dose topical ocular studies were conducted in rabbits up to nine months and monkeys for up to three months with the approved 1 mg/ml formulation. Repeat dose systemic oral studies were also conducted with nepafenac for up to six months in rats. Study reports from the systemic evaluations were submitted at the time of the initial marketing authorisation application.

In order to demonstrate the safety of nepafenac 3 mg/ml eye drops, suspension, a one-month repeat-dose topical ocular study was conducted in pigmented rabbits. This study rabbits did not show any systemic or topical ocular toxicity.

Toxicokinetic data

Toxicokinetic data were provided from a one-month repeated-dose topical ocular study in rabbits. This study also included a vehicle arm to investigate ocular toxicity of the guar derivative HP guar.

The results of this study showed an increase in exposure as the total daily dose was increased (measured by AUC_{0-3h}), although the increase in C_{max} was not linear across the entire dose range. No accumulation was observed for amfenac or nepafenac. No ocular adverse effects were seen in the HP guar vehicle arm.

In addition, following a query from the CHMP, the MAH presented a summary of a previously submitted 3-month study in rabbits including groups treated with the currently marketed concentration of nepafenac (1 mg/ml) and the proposed concentration 3 mg/ml). In this study, nepafenac ophthalmic suspension up to a concentration of 10 mg/ml did not induce any significant ocular irritation or systemic toxicity following three months of daily QID topical administration.

Genotoxicity, carcinogenicity, reproduction toxicity, local tolerance and other toxicity studies

Genotoxicity, reproductive and developmental toxicity studies, local tolerance, antigenicity and phototoxicity studies were submitted previously. Carcinogenicity studies were not conducted by the MAH.

2.3.5. Ecotoxicity / environmental risk assessment

In line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 1*), the MAH presented the results of calculations to estimate the exposure with nepafenac. Nepafenac predicted environmental concentration (PEC) was calculated at a PEC surfacewater value of 1.05·10-3 µg/ml, which is below the action limit of 0.01 µg/L. Therefore, in line with the Guideline, no further environmental fate and effects analysis were conducted.

In addition, nepafenac is not considered a persistent, bioaccumulative and toxic (PBT) substance (log Kow does not exceed 4.5).

2.3.6. Discussion on non-clinical aspects

The existing and new pharmacodynamic studies support an anti-inflammatory action of the new 3 mg/ml formulation. While no new safety pharmacology studies were performed, the studies submitted at the time of the initial marketing authorisation demonstrated that nepafenac concentrations multiple times higher than the maximum daily therapeutic dose did not result in systemic effects including neuropharmacological signs, pro-convulsant effects, hemodynamic or ECG effects. In a Scientific Advice from 17 December 2009 (EMEA/H/1405/1/2009/III) the CHMP confirmed that there is no need to conduct any further safety pharmacology studies for the marketing application of nepafenac 3 mg/ml eye drops, suspension.

The lack of pharmacodynamic interaction studies was considered by the CHMP justified taking into account the low systemic exposure to nepafenac in humans.

The non-clinical pharmacokinetics of nepafenac and amfenac have been established and were previously submitted at the time of the initial marketing authorisation application of Nevanac. Additional tissue distribution studies showed that a single dose of nepafenac ophthalmic suspension 3 mg/ml resulted in higher exposure of nepafenac and amfenac in the ocular tissue (except for the lens) as compared to 1 mg/ml TID, which could be expected.

The CHMP noted that the MAH did not include in the toxicokinetic study a group of animals treated with the currently marketed formulation, as was recommended in the Scientific Advice issued by CHMP in December 2009 (EMEA/H/1405/1/2009/III), and therefore no toxicokinetic comparison between the new 3 mg/ml formulation and the existing formulation could be made. However, due the lack of ocular irritation or systemic toxicity observed in any of the topical studies performed previously at any concentration, the CHMP concluded that the lack of a comparison group could be accepted.

The CHMP also noted that no ocular adverse effects were seen in the vehicle arm with the new excipient HP guar. Guar has been extensively used in foods, some pharmaceutical preparations and cosmetics. The derivative HP guar has been used in a topical ophthalmic formulation in the EU for about eight years without any significant adverse report, which was considered reassuring by the CHMP.

Based on the chemical class, short duration of therapy, low systemic exposure potential, and non-clinical toxicology study results which showed no evidence of preneoplasic lesions in rats, the CHMP concluded that the absence of carcinogenicity studies as well as other toxicology studies was justified.

As for environmental risk assessment, the predicted environmental concentration of nepafenac was below the action level and is not considered a PBT (persistent, bioaccumulative and toxic) substance. Therefore, in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 1*), without the need for further analyses, the CHMP considered that the new nepafenac formulation is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data base, including limited new results from pharmacology, tissue distribution and toxicology studies as well as previously submitted study data, was considered by the CHMP as sufficient to support the application for the new 3 mg/ml formulation of nepafenac.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development of nepafenac 3 mg/ml eye drops, suspension, consisted of the following studies:

- A new **clinical pharmacology study (C-09-053)** conducted in healthy subjects to assess the systemic pharmacokinetics of nepafenac at the intended dosing. A number of studies included in the original dossier for the 1 mg/ml formulation were also submitted.
- Two clinical trials to support the efficacy and safety of the intended formulation in the applied indication: **Study C-09-055 (pivotal trial)** primarily aimed at establishing non-inferiority between the new 3 mg/ml formulation and the currently available 1 mg/ml formulation; and **study C-11-003 (supportive study)** intended to demonstrate the superiority of nepafenac with respect to placebo.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

A new clinical pharmacology study in healthy subjects (Study C-09-053) has been presented in the current submission to evaluate the systemic pharmacokinetics of nepafenac 3 mg/ml at the intended dosing.

Relevant information from other clinical pharmacology studies included in the original dossier submitted with the marketing authorisation application for the 1 mg/ml formulation [three times a day (TID) dosing] (Study C-04-08) were also referred to.

Study C-09-053

- Study design and objectives:

This phase I study was a single centre, randomised, double-masked, vehicle-controlled, parallel-group study.

The primary objective of this study was to assess the systemic pharmacokinetics of nepafenac and its pharmacologically active metabolite (amfenac) after a single dose of nepafenac ophthalmic suspension, 3 mg/ml and at steady-state following once daily topical ocular dosing for 4 days in healthy subjects. The secondary objective was to assess the safety of nepafenac ophthalmic suspension, 3 mg/ml following once daily dosing for 4 days in healthy subjects.

All 20 enrolled healthy subjects were randomised to nepafenac ophthalmic suspension, 3 mg/ml or nepafenac ophthalmic suspension vehicle. Subjects were dosed on the morning of day 1 and administered subsequent doses through day 4 at the appropriate intervals to comply with the dosing regimen. Participants were administered once daily bilateral topical ocular doses of 1 drop/eye of Nepafenac Ophthalmic Suspension, 3 mg/ml. The last pharmacokinetic blood sample was taken on the morning of day 5.

- Demographics

All study subjects were 18-64 years of age (mean = 37.6 years), were equally distributed by sex, and were primarily White (70%); there were no statistical differences between treatment groups based on demographic characteristics and all randomized subjects completed the trial.

All 12 subjects in the active treatment arm were included in the pharmacokinetic data set; all 20 study participants were included in the safety data set.

- Results

Pharmacokinetics

Nepafenac reached a mean maximum plasma concentration (C_{max}) of 0.921 ng/ml on day 1, and 0.847 ng/ml on Day 4. The mean exposure, as measured by AUC_{0-t} was 1.50 ng*hr/ml on day 1 and 1.34 ng*hr/ml on day 4. The median half-life ($t_{1/2}$) was 0.85 hours on day 1 and 0.74 hours on day 4. The mean C_{max} was below limit of quantitation at 8 hours (of a 24 hour dosing interval) both on day 1 and day 4.

For amfenac the mean maximum plasma concentrations (C_{max}) were 1.15 ng/ml on day 1, and 1.13 ng/ml on day 4. The mean exposure (AUC_{0-t}) was 3.28 ng*hr/ml on day 1 and 3.33 ng*hr/ml on day 4. The median half-life ($t_{1/2}$) was 5.49 hours on day 1 and 6.26 hours on day 4, and the mean C_{max} was below limit of quantitation at 12 hours (of a 24-hour dosing interval) on day 1 and day 4.

Safety

A total of 3 adverse events were reported in 2 (16.7%) subjects in the nepafenac 3 mg/ml group. These adverse events included vessel puncture site hematoma and vessel puncture site pain (1 subject experienced separate vessel puncture site pain adverse events for each arm). These events were mild in intensity and not serious. A total of 5 adverse events were reported in 3 (37.5%) subjects in the vehicle group (nausea, vessel puncture site pain, and syncope, all reported by the same individual subject; and vessel puncture site hematoma, reported by 2 individual subjects). Across both treatment groups, none of the reported adverse events were considered drug-related and all were considered nonocular.

Comparison and analyses of results across studies: Nepafenac 3 mg/ml (study C-09-053) vs Nepafenac 1 mg/ml (study C-04-08)

Study C-04-08 was similar to study C-09-053. Nepafenac 1 mg/ml was administered to both eyes three times a day (TID) for 3 days with a final dose on the morning of day 4. Twenty subjects (randomised 16:4 to active and vehicle treatment, respectively) with ages ranging from 18 to 52 years were enrolled in the study.

When exposures of nepafenac and amfenac were compared across studies between nepafenac 1 mg/ml (C-04-08) given three times daily (TID) versus nepafenac 3 mg/ml (C-09-053) given once daily (QD) in healthy subjects, a dose proportional increase in exposures was observed after day 4 with nepafenac 3 mg/ml (see table Table 1): a 3-4 fold increase in C_{max} and AUC was observed for both nepafenac and its metabolite amfenac. Furthermore, an extension of the amfenac elimination half-life was detected (6.26 hours for 3 mg/ml formulation QD vs 1.6 hours for 1 mg/ml TID) that appears attributable to quantifiable concentration observed over longer time points with nepafenac 3 mg/ml.

Table 1: Comparison of Mean (SD)/Range Pharmacokinetic Parameters of Nepafenac and Amfenac after Multiple Doses (Day 4) of NEVANAC 1 mg/ml (0.1%)(Study C-04-08) versus Nepafenac 3 mg/ml (0.3%) (Study C-09-053) in Healthy Subjects

PK Parameters	AL-6515		AL-6295	
	NEVANAC 0.1% TID (N = 16)	Nepafenac 0.3% QD (N = 12)	NEVANAC 0.1% TID (N = 16)	Nepafenac 0.3% QD (N = 12)
C_{max} (ng/mL)	0.310 (0.104)	0.847 (0.269)	0.422 (0.121)	1.13 (0.419)
T_{max} (h)	0.25 (0.17 – 0.50)	0.42 (0.33 – 0.75)	0.55 (0.33-0.83)	0.75 (0.50 – 1.00)
AUC_{0-t}[b] (ng*h/mL)	0.368 (0.106)	1.34 (0.522)	0.976 (0.284)	3.33 (1.31)
$AUC_{0-\infty}$ (ng*h/mL)	0.371 (0.109)	1.43 (0.533)	1.03 (0.314)	3.70 (1.43)
$t_{1/2}$ (h)	0.9 (0.7-1.6)	0.74 (0.49 – 1.85)	1.6 (1.2-2.3)	6.26 (3.28 – 10.55)

[b]t refers to the last quantifiable concentration measured following dosing on Day 4

2.4.3. Pharmacodynamics

No specific pharmacodynamic studies in humans have been performed to support this application. Additional data were available from non-clinical pharmacodynamic studies (see chapter 2.3.) and from clinical pharmacodynamic studies performed to support the initial marketing authorisation application.

2.4.4. Discussion on clinical pharmacology

The administration of 3 mg/ml nepafenac QD reached low systemic concentration of nepafenac and amfenac, being quantifiable up to 8 and 12 hours post-dose, respectively. No signs of accumulation after repeated (daily) dosages were observed and no relevant safety concerns were reported.

Given that a comparison of the relationship between plasma concentration and effect for the two regimens of dosage (nepafenac 3 mg/ml QD versus nepafenac 1 mg/ml TID) is not available, it is not possible to estimate whether the intended dosage will sufficiently cover the 24-hour time during the cataract postoperative period.

A comparison of the new 3 mg/ml formulation QD and the currently available formulation (nepafenac 1 mg/ml TID) is only available by indirect means based on an inter-study comparison, showing a dose proportional increase in exposures with nepafenac 3 mg/ml. The CHMP agreed that no conclusions on a potential clinical benefit could be drawn based solely on this greater exposure with the new formulation.

2.4.5. Conclusions on clinical pharmacology

The CHMP noted the limited information on clinical pharmacology for nepafenac 3 mg/ml, eye drops, suspension.

No specific pharmacodynamic studies in humans have been performed to support this submission. However, evidence was available from non-clinical studies supporting an anti-inflammatory mode of action of the new 3 mg/ml formulation.

The systemic pharmacokinetics of nepafenac at the intended dosing has been evaluated in healthy subjects, showing low systemic exposure and lack of accumulation of nepafenac after repeated administration. No relevant safety concerns have been raised.

Overall, the CHMP considered the available clinical pharmacology data as sufficient to support the application for the new 3 mg/ml formulation.

2.5. Clinical efficacy

2.5.1. Main studies

The clinical development plan to demonstrate efficacy of nepafenac 3 mg/ml eye drops, suspension for the prevention and treatment of pain and inflammation associated with cataract surgery consisted of 2 multicentre, randomised, double-masked, parallel-group, vehicle and active-controlled clinical trials.

Study C-11-003 (phase 2) was aimed at demonstrating the superiority of nepafenac 3 mg/ml over placebo (vehicle) while the main objective of the **Study C-09-055** (phase 3) was to establish the comparability (non-inferiority) between nepafenac 3 mg/ml and nepafenac 1 mg/ml. These studies involved both US and EU population.

Table 2: Overview of clinical trials for nepafenac 3 mg/ml (0.3%) eye drops, suspension

Study Identifier / Study Type	Study Design	Study Population	Treatment Group	Number of Patients[a]	Dosing Regimen	Dosing Duration
C-11-003 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	• Nepafenac 3 mg/mL QD • Nepafenac 0.1% QD • Vehicle QD	522 506 254	1 drop in study eye QD beginning 1 day before surgery. An additional drop was administered 30 to 120 minutes prior to surgery	16 days
C-09-055 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	• Nepafenac 3 mg/mL QD • NEVANAC TID • Vehicle QD • Vehicle TID	807 813 197 205	1 drop in study eye QD or TID, as assigned, beginning 1 day before surgery. An additional drop was administered 30 to 120 minutes prior to surgery	16 days

[a] Safety dataset Placebo = Vehicle QD = once daily TID = 3 times daily

2.5.1.1. Methods

Objectives

Study C-09-055

The primary efficacy objectives of study C-09-055 were to demonstrate that for the prevention and treatment of ocular inflammation 14 days after cataract extraction:

- Nepafenac 3 mg/ml dosed once daily is non-inferior to nepafenac 1 mg/ml dosed 3 times daily,
- Nepafenac 3 mg/ml dosed once daily is superior to vehicle (3 mg/ml) dosed once daily,
- Nepafenac 1 mg/ml dosed 3 times daily is superior to vehicle (1 mg/ml) dosed 3 times daily.

Secondary efficacy objectives were to demonstrate that for the prevention and treatment of ocular pain 14 days after cataract extraction:

- Nepafenac 3 mg/ml dosed once daily is non-inferior to nepafenac 1 mg/ml dosed 3 times daily,
- Nepafenac 3 mg/ml dosed once daily is superior to vehicle (3 mg/ml) dosed once daily,
- Nepafenac 1 mg/ml dosed 3 times daily is superior to vehicle (1 mg/ml) dosed 3 times daily.

Study C-11-003

The primary objective of study C-11-003 was to demonstrate that nepafenac 3 mg/ml is superior to nepafenac vehicle 3 mg/ml, each used once daily, for the prevention and treatment of ocular inflammation with respect to cure rate 14 days after cataract extraction.

The secondary objective of this study was to demonstrate that nepafenac 3 mg/ml is superior to nepafenac 1 mg/ml, each used once daily, for the prevention and treatment of ocular inflammation with respect to cure rate 7 days after cataract extraction.

Study participants

Adult patients (18 years or older) of either race and sex, requiring cataract extraction by phacoemulsification with planned implantation of a posterior chamber intraocular lens were eligible to be enrolled.

Sample size

Study C-09-055

Previous studies of nepafenac in the same indication were used to predict cure rates in these studies (assumed cure rates were 70% for nepafenac 3 mg/ml and 50% for the vehicle). In addition, a non-inferiority margin of 10% was used. It was furthermore assumed that 90% of the patients randomised would be evaluable for the respective analyses.

The planned sample size in study C-09-055 was 2000 patients, 800 patients in each nepafenac group and 200 patients in the corresponding vehicle groups.

Study C-11-003

Previous studies of nepafenac in the same indication were used to predict cure rates in these studies. The planned sample size was 1250 patients (500 patients in each nepafenac group and 250 patients in the vehicle group).

Treatments

Patients were treated in the operative eye for 16 days. Dosing started 1 day prior to surgery, continued on the day of surgery and for 14 days following surgery. One additional drop of the study medication was administered 30 to 120 minutes prior to surgery.

Physicians were allowed to choose to extend therapy to 21 days depending on individual patient response.

Topical ocular instillation of medication in the form of eye drops does not allow a precise evaluation of patient compliance to treatment. Assessment of drug concentration in plasma samples was not conducted.

Outcomes/endpoints

Efficacy variables

Both studies assessed **ocular inflammation** as the main outcome defined by aqueous cells and flare scores. Aqueous cells and flare were evaluated using slit-lamp biomicroscopy and were graded by the investigator on 5-point scale for cells (0: no cells, 1: 1 to 5 cells, 2: 6 to 15 cells, 3: 16 to 30 cells, 4: greater than 30 cells) and a 4-point scales for flare (0: no visible flare, 1: mild flare, 2: moderate flare, 3: severe, very dense flare).

Inflammation was assessed at each post-surgical visit, scheduled for Days 1, 3, 7 and 14, at the early exit and any unscheduled visits. The variable was a composite, requiring a score of 0 for both cells (0 cells present) and flare (no flare present). A binary variable of cure for inflammation was both primary and secondary efficacy in this study.

A subjective assessment of **ocular pain**, rated on a 6-point scale by the investigator during the examination was utilised in both of the efficacy studies. The scale also served as a criterion for determining treatment failures.

Primary variable

Proportion of patients who were declared a cure at day 14. Cure was defined based on a composite endpoint requiring as a score of 0 for both aqueous cells and aqueous flare.

Secondary variables

Proportion of patients who were pain-free, defined by ocular pain assessment score of 0.

The following endpoints were included as secondary variables in study C-11-03 and as supportive variables in study C-09-055:

- cumulative percentage of cures by visit
- cumulative pain-free rates by visit

For both variables of cumulative cures, in order to meet this requirement, a patient who was judged to be cured must have remained cured at all subsequent visits. In the event that a patient was considered a cure prior to day 14 and missed subsequent visits, a last observation carried forward approach was used and the patient was considered a cure at subsequent visits.

- proportion of patients who were declared a treatment failure, defined as aqueous cells score ≥ 3 (16 or more cells), aqueous flare score of 3 (severe), and/or ocular pain score ≥ 4 (moderately severe pain).

Because the use of acetaminophen was allowed by protocol, a sensitivity analysis was performed that compared the proportion of patients who had ocular pain or who took acetaminophen within 48 hours prior to assessment to the proportion of patients who were pain-free and did not take acetaminophen within 48 hours prior to assessment.

- proportion of patients who were a clinical success, defined as cells score ≤ 1 (0-5 cells) and flare score = 0. This was an unplanned analysis.

In addition, study C-09-055 included the following secondary variable: Proportion of patients who were pain-free, defined by ocular pain assessment score equals zero.

Safety variables

The safety variables in these studies were adverse events (incidence of adverse events), best-corrected visual acuity, IOP, slit-lamp parameters (chemosis, bulbar conjunctival injection, corneal oedema), and dilated fundus parameters (retina/macula/choroid, optic nerve).

The safety analyses consisted of descriptive summaries of the data as relevant to the scale of data, eg, frequency and percentage for adverse events, and mean changes from baseline as appropriate.

Randomisation

Patient randomisation was conducted through a secure web interface with stratification by study site to ensure balanced treatment assignment at each site (2:2:1 ratio in Study C-11-003 and 4:4:1:1 in Study C-09-055).

Blinding (masking)

The studies were double-masked. The sponsor, and monitors involved in reporting, obtaining, and/or reviewing the clinical evaluations were not aware of the specific treatment being administered. Only once all study data were verified, validated, and the database locked, were individual patients unmasked. The randomization code was not broken during the conduct of this study.

Statistical methods

Both studies

All randomised patients with at least 1 postoperative on-therapy assessment (including those who discontinued as treatment failures) were evaluable for the intent-to-treat (ITT) analysis data set. This was the primary analysis data set for determining efficacy.

A per protocol (PP) analysis data set was defined to include patients in the ITT analysis data set who met all inclusion/exclusion criteria that may have affected efficacy assessments, took test article according to treatment assignment, and had a visit at Day 14 or discontinued the study as a treatment failure.

Study C-09-055

For comparison of the 2 active treatment groups, a 2-tailed 95% confidence interval was calculated for the difference in cure rates at day 14. The non-inferiority margin was 10 percentage points.

For comparison of active versus vehicle treatment groups, the Cochran-Mantel-Haenszel test was used (5% significance level, 2-sided).

Study C-11-003

The primary and secondary analyses used Cochran-Mantel-Haenszel tests controlling for investigative site to assess differences between treatment groups at alpha level of 0.05.

2.5.1.2. Results

2.5.1.2.1. Study C-09-055 (pivotal trial)

A total of 2120 patients were enrolled in this study. Of these, 2022 patients were included in the ITT analysis. A total of 1962 patients enrolled were included in the PP analysis. Overall, 1750 patient completed the study and 272 discontinued. Nearly half of the patients in the vehicle group discontinued early. The majority of discontinuations was due to treatment failure and occurred more frequently in the 3 mg/ml and 1 mg/ml vehicle groups (32.7% and 30.0%, respectively) than in the active treatment arms (2.9% and 3.8% for nepafenac 3 mg/ml and 1 mg/ml, respectively).

Patients recruited were predominantly elderly (over 70%). The mean age of study participants was around 69 years.

- *Primary efficacy variable*: Percentage of cures of ocular inflammation at day 14

At day 14, 68.4% and 70% of patient receiving nepafenac 3 mg/ml and 1 mg/ml (NEVANAC), respectively, were considered cured (see Figure 1). The lower bound of the 95% 2-sided confidence interval (-5.73%, 3.17%) is greater than -10%. Therefore, nepafenac 3 mg/ml (3 mg/ml) dosed once daily can be considered non-inferior to nepafenac 1 mg/ml (0.1%) dosed 3 times daily as regards ocular inflammation (primary non-inferiority endpoint).

- **Figure 1: Percentage of patients cured at day 14 (ITT)**

Nepafenac 0.3%		NEVANAC		Vehicle 0.3%		Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	552 (68.4)	811[a]	568 (70.0)	197	67 (34.0)	205	73 (35.6)	< 0.0001	< 0.0001

Cure is defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing post surgery data.
n is the number of patients cured.
% is calculated as (n/N)*100.
[a]2 patients were randomized but did not have on-study data.
p-value is based upon Cochran-Mantel-Haenszel test controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

Furthermore, the difference between the cure rates of active versus vehicle groups at day 14 was statistically significant ($p < 0.0001$) for both nepafenac 3 mg/ml and nepafenac 1 mg/ml (primary superiority endpoint).

The PP analysis was similar to the ITT analysis for both primary non inferiority and superiority efficacy results.

- *Secondary efficacy variable:* Percentage of patients with no ocular pain at day 14

Figure 2 shows that at day 14 post operation, a similar percentage of patients reported no ocular pain in the two active treatment arms (31% and 90.9%, respectively). The lower bound of the 95% 2-sided confidence interval (-3.08%) is greater than -10%; therefore, the secondary noninferiority efficacy results show that nepafenac 3 mg/ml is noninferior to nepafenac 1 mg/ml as regards ocular pain.

Secondary superiority efficacy results show that nepafenac 3 mg/ml and nepafenac 1 mg/ml are superior to their respective vehicles for the treatment of ocular pain as assessed by the investigator 14 days after cataract extraction, $p < 0.0001$.

Figure 2: Percentage of pain-free patients at day 14 (ITT)

Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	734 (91.0)	811[a]	737 (90.9)	197	98 (49.7)	205	115 (56.1)	< 0.0001	< 0.0001

Pain-free is defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing post surgery data.
n is the number of patients pain-free.
% is calculated as (n/N)*100.
[a]2 patients were randomized but did not have on-study data.
p-value is based upon Cochran-Mantel-Haenszel controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

The PP analysis was similar to the ITT analysis.

- *Supportive variables*

Percentage of cumulative cures by visit

A statistically significant difference in the cumulative percentage of patients who were considered cured was observed for nepafenac 3 mg/ml compared with vehicle 3 mg/ml beginning on day 7

postoperatively (p<0.0001). For nepafenac 1 mg/ml compared to vehicle, a statistically significant difference was observed as of day 3 visit (p<0.0001).

Cumulative pain-free rates by visit

There was a statistically significant difference between the nepafenac 3 mg/ml study arm compared with the vehicle 3 mg/ml group with regards to the cumulative percentage of patients who were pain-free at all postoperative visits (p<0.0001). This same difference was observed for nepafenac 1 mg/ml when compared to its vehicle.

Percentage of treatment failures

The percentage of patients who were treatment failures at any time during the study was smaller in the nepafenac 3 mg/ml group than in the vehicle 3 mg/ml group (day 14: 3.2% and 35.0%, respectively, p<0.0001). A similar result was observed in the nepafenac 1 mg/ml group versus the 1 mg/ml vehicle group (day 14: 4.4% and 31.2%, respectively, p<0.0001).

2.5.1.2.2. Study C-11-003 (supportive trial)

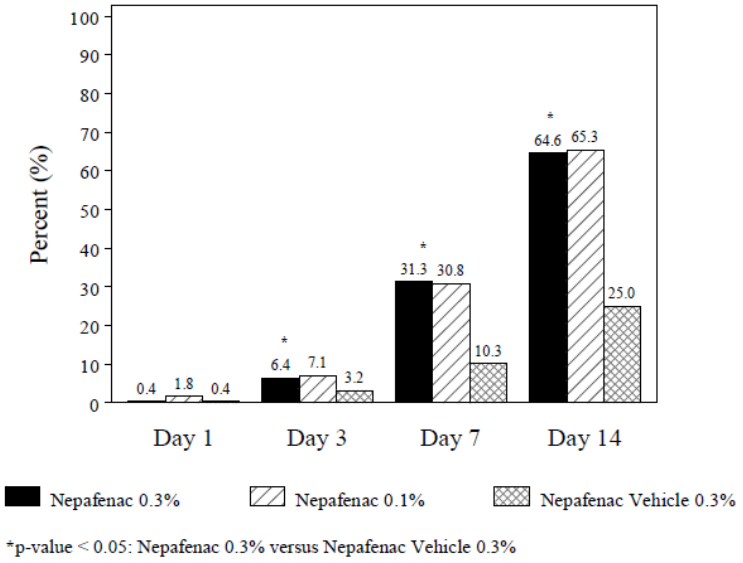
A total of 1,342 patients (512 in nepafenac 3 mg/ml, 493 in nepafenac 1 mg/ml and 252 in vehicle group) were enrolled in this study. The number of enrolled patients who completed the study was 475, 458 and 121, respectively. Overall, 288 (21.5%) patients discontinued early. Overall, 12.0% and 14.2% of patients receiving nepafenac 3 mg/ml and 1 mg/ml, respectively, discontinued early, while the discontinuation rate in the vehicle groups was 54.9%. The majority of patients on vehicle discontinued due to treatment failure (37.7%). Among all patients enrolled, the most common reason for study discontinuation was treatment failure (10.4%) followed by patient did not use study medication (4.5%), other (2.9%), and adverse events (2.5%).

The mean age of study participants was around 69 years ranging from 21 to 94 years.

- *Primary efficacy variable:* Percentage of cures at day 14

Primary efficacy results showed that nepafenac 3 mg/ml was superior to its vehicle (64.6% vs 25%; p<0.0001) for treatment of ocular inflammation at the day 14 visit following cataract extraction (primary endpoint).

Figure 3: Cumulative percentage of cures by visit (ITT)



*p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

- *Secondary efficacy variables:*

Cumulative percentage of cures by visit

There was no significant difference between the nepafenac 3 mg/ml and the nepafenac 1 mg/ml arm (31.3% vs 30.8%; p= 0.9805) with regards to the cumulative percentage of cures at the day 7 visit following cataract extraction (see also Figure 3; secondary endpoint).

Cure rates were generally similar between the 2 nepafenac groups.

Nepafenac 3 mg/ml was superior to its vehicle beginning day 3 postoperatively (p = 0.0367 at day 3, and p < 0.0001 days 7 and 14).

Cumulative percentage of pain-free patients by visit

There was a significant difference at all visits for nepafenac 3 mg/ml compared to nepafenac vehicle 3 mg/ml for the cumulative percentage of patients who were pain-free.

Percentage of treatment failures by visit

Fewer patients were treatment failures in the nepafenac 3 mg/ml treatment group compared to nepafenac vehicle 3 mg/ml treatment group (4.5% vs 40.5%; p < 0.0001).

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The CHMP noted that only study C-09-055 included nepafenac 1 mg/ml, TID, in line with the approved posology, as active comparator. Study C-11-003 in which nepafenac 1 mg/ml is dosed QD was considered as supportive for this application.

The applied methods to measure inflammation and pain (with little variations) have been previously used in the clinical development of nepafenac 1 mg/ml and other topical ophthalmic NSAIDs for the same indication and were considered acceptable by the CHMP.

Patients recruited in both studies were predominantly elderly (over 70%) and were considered by the CHMP to be representative of the target population undergoing cataract surgery. Demographics

characteristics were essentially balanced at baseline among the different groups of comparison.

The studies were designed to be blindly assessed for efficacy. However, the CHMP pointed out that in study C-09-055 some patients received the treatment once daily (nepafenac 3 mg/ml and its vehicle groups) and other patients were treated three times a day (nepafenac 1 mg/ml and its vehicle group). However, as each active study drug and its vehicle were separately compared, the CHMP agreed that blindness was ensured.

While in both studies, 14 days postoperative treatment was the minimum recommended duration of therapy in both studies and was used for the efficacy assessment, the CHMP noted that only few patients received treatment beyond this point and up to 21 days post surgery. The Committee concluded that since the proposed treatment recommendation is for short term therapy up to 3 weeks post surgery based on the physician's judgement, the proposal could be acceptable. However, the CHMP recommended including a cross reference to section 5.1 in section 4.2 of the SmPC to refer to the limited available data.

The CHMP noted that the number of patients who completed the studies was impacted by the failures of the treatment. Whereas the retention of patients was high in the active treatment groups, about 50% of patients on vehicle discontinued early, mostly due to treatment failure. The CHMP considered that it was uncertain whether this issue had an impact on the results considering the already uneven numbers of patients in the comparison groups. However, the CHMP acknowledged that the differences in retention between active and vehicle treatment arms might be indicative of the efficacy of nepafenac 1 mg/ml and 3 mg/ml. The replication of these results in previous studies and the similar behaviour of the two placebo (vehicle) arms reinforce the consideration of the observed effect as a true (not biased) one.

Efficacy data and additional analyses

The CHMP noted that in both studies patients treated with nepafenac 3 mg/ml QD showed a statistically significant higher rate of cure 14 days after surgery (absence of inflammation signs) than those receiving vehicle. The signs of inflammation disappeared faster in the nepafenac 3 mg/ml group than in the vehicle group. Furthermore, significantly fewer patients on nepafenac 3 mg/ml reported any grade of pain during the 2 week period following surgery when compared to patients on vehicle.

When both strengths were compared (pivotal trial C-09-055: nepafenac 3 mg/ml QD vs nepafenac 1 mg/ml TID), non-inferiority of nepafenac 3 mg/ml relative to nepafenac 1 mg/ml was demonstrated. Nepafenac 1 mg/ml (the reference product) reached a cure rate of ocular inflammation similar to that previously described. Therefore the CHMP considered that both formulations and posologies render a similar anti-inflammatory effect after 14 days post cataract extraction. Patients treated three times a day with nepafenac 3 mg/ml showed slightly better results in the treatment of ocular inflammation than those receiving the dose once daily, but these numerical differences were not considered clinically relevant by CHMP.

The CHMP furthermore noted that non-inferiority between the two formulations was also demonstrated in the control of pain.

When nepafenac 3 mg/ml was compared to nepafenac 1 mg/ml (both dosed once daily) in the supportive trial C-11-003, no clinically relevant and statistically significant differences on the resolution of the inflammation and the control of pain were observed. The CHMP however recognised that the comparison between nepafenac 3 mg/ml QD and nepafenac 1 mg/ml QD is of little use since the comparator is not administered at the recommended dose. Furthermore, rather than putting into question the efficacy of the new 3 mg/ml formulation, the results suggest that nepafenac 1 mg/ml might already be effective when administered once daily.

Finally, the CHMP considered that the proposed new formulation contains a carbopol-guar vehicle to enhance ocular retention. Whether this excipient may have any influence on the global effect of nepafenac 3 mg/ml is unknown. Although the potential effect of the excipient guar in the efficacy of nepafenac has been scarcely justified by the MAH, the CHMP was of the opinion that the available data don't give rise to any concern at the time of this report. Both vehicles had shown similar results when they were indirectly compared.

2.5.3. Conclusions on the clinical efficacy

Superiority of nepafenac over placebo (vehicle) in the prevention and treatment of inflammation and pain following cataract surgery was demonstrated in both clinical trials. No relevant differences between treatments were seen for the inflammatory assessment and pain resolution when nepafenac 3 mg/ml QD and nepafenac 1 mg/ml TID were compared.

Overall, the CHMP was of the opinion that the available data demonstrated efficacy of the new nepafenac 3 mg/ml formulation in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery.

2.6. Clinical safety

The safety analysis of Nepafenac 3 mg/ml eye drops, suspension was based on the results obtained from the following 3 studies:

- two post-cataract ocular inflammation clinical studies (**C-09-055 and C-11-003**)
- one phase 1 pharmacokinetic study (**C-09-053**)

The primary evaluation of safety from clinical trials involved in the development of nepafenac 3 mg/ml eye drops, suspension is based on the safety parameters assessed during the post-cataract ocular inflammation studies (C-09-055 and C-11-003). Information collected from the pharmacokinetic study is considered as supportive safety data.

The evaluation of safety was conducted on all randomised patients who received at least 1 dose of the study drug.

The safety assessment included the extent of exposure to study drug, adverse events and other safety related parameters, including best corrected visual acuity, ocular signs (corneal oedema, bulbar conjunctival injection, and chemosis), intraocular pressure, and dilated fundus parameters (retina/macula/choroid, and optic nerve).

Clinical laboratory measurements (i.e. hematology, blood chemistry and urinalysis) were only conducted in a small subset of patients and healthy subjects (N=20). No laboratory examinations were conducted in clinical trials in post-cataract surgery patients. Moreover, non-ocular vital signs and physical findings were not monitored in any of the clinical studies.

Patient exposure

The development programme integrated a total of 3344 patients, which included 1351 subjects exposed to nepafenac 3 mg/ml eye drops, suspension. Among the patients exposed to the active substance, 1339 subjects matched the intended target population (post-cataract surgery patients) that received nepafenac at the claimed dosing schedule (3 mg/ml QD). Therefore, they were considered as the appropriate safety population for the overall safety analysis.

Duration of exposure was generally below 16 days. Amongst the patients treated with nepafenac 3

mg/ml QD 49.3% of patients were exposed between 10-16 days and 44.1% were exposed more than 16 days.

Adverse events

The majority of adverse events were local ocular adverse events. In addition, systemic adverse events such as headache, hypertension, back pain, toothache and pain were also observed. The most frequently adverse events reported during post-cataract inflammation studies in nepafenac 3 mg/ml versus nepafenac 1 mg/ml were headache (2.0% vs 1.6%) and increased intraocular pressure (1.1% vs 0.9%).

Concerning treatment related adverse events, three adverse drug reaction (ADR) were reported in the nepafenac 3 mg/ml treatment group with no ADRs reported among the other active treatment groups (see Figure 4). The 3 ADRs reported were eye pain, punctate keratitis (both mild in intensity and resolved without treatment and not causing patient discontinuation) and hypersensitivity (allergic reaction on the face, moderate in intensity, resolved with treatment and causing discontinuation).

Figure 4: Treatment-Related Adverse Events (C-09-055 and C-11-003)

	Nepafenac 3 mg/mL N=1339		NEVANAC N=819		Nepafenac 1mg/mL QD N=506		Nepafenac Vehicle 3 mg/mL N=455		NEVANAC Vehicle N=205	
Coded Adverse Event	N	%	N	%	N	%	N	%	N	%
Related										
Eye disorders										
Eye pain	1	0.1							1	0.5
Eyelid oedema							1	0.2		
Foreign body sensation in eyes							1	0.2		
Punctate keratitis	1	0.1								
Immune system disorders										
Hypersensitivity	1	0.1								

Coded adverse event = MedDRA Preferred Term (version 14.0) presented by System Organ Class.

Concerning select treatment emergent adverse events, Figure 5 provides an overview of the observed events.

Figure 5: Select Treatment Emergent Adverse Events (C-09-055 and C-11-003)

Coded Adverse Event	Nepafenac 3 mg/mL (N = 1339) N (%)	NEVANAC (N = 819) N (%)	Nepafenac 1mg/mL QD (N=506) N (%)	Nepafenac Vehicle 3 mg/mL (N =455) N (%)	NEVANAC Vehicle (N = 205) N (%)
Eye disorder					
Corneal oedema	6 (0.4)	--	1 (0.2)	6 (1.3)	2 (1.0)
Punctate keratitis	3 (0.2)	2 (0.2)	--	--	--
Corneal epithelium defect	--	1 (0.1)	--	1 (0.2)	--
Keratopathy	1 (0.1)	1 (0.1)	--	--	--
Corneal epithelial microcysts	1 (0.1)	--	--	--	--
Keratitis	--	1 (0.1)	--	--	--
Conjunctival haemorrhage	5 (0.4)	2 (0.2)	2 (0.4)	1 (0.2)	--
Retinal haemorrhage	2 (0.1)	--	--	--	--
Injury, poisoning, and procedural complications					
Corneal abrasion	6 (0.4)	1 (0.1)	--	1 (0.2)	1 (0.5)
Investigations					
Intraocular pressure increased	15 (1.1)	7 (0.9)	1 (0.2)	1 (0.2)	--
Nervous system disorders					
Headache	27 (2.0)	13 (1.6)	6 (1.2)	5 (1.1)	3 (1.5)
Includes all events (Related + Not Related, combined)					

Serious adverse event / deaths / other significant events

No deaths and no serious adverse events were reported in any study.

2.6.1. Discussion on clinical safety

The CHMP noted the limited data for patient exposure beyond day 14 post operation (see also discussions on efficacy in chapter 2.5.2.). However, the CHMP concluded that since the MAH has proposed short-term duration of treatment (21 days), the overall exposure is deemed as sufficient. Long-term safety beyond this period is at present uncertain, but the Risk Management Plan (RMP) already includes a safety concern to this end.

With regards to the preservative benzalkonium chloride, which has been reported to cause ocular events (punctate keratopathy and/or toxic ulcerative keratopathy), the CHMP noted that the new proposed formulation and posology (QD) may have a theoretical advantage in comparison to the approved 1 mg/ml formulation, as the latter has to be applied three times a day and therefore results in a higher exposure of the preservative. However, no difference in the frequency of adverse events was observed that would support an advantage with regards to safety of the new formulation over the approved one.

As already discussed in the context of the efficacy data, the guar excipient, which is used to increase viscosity has never been used in a centrally authorised ophthalmic medicinal product. The CHMP noted that the potential effect of this excipient on the safety of the new formulation has hardly been discussed by the MAH in the application. However, as was concluded with regards to

efficacy, given that both 3 mg/ml and 1 mg/ml vehicles had shown similar results when indirectly compared in the pivotal trial and no safety concerns had been observed regarding the non-clinical study in rabbits, the CHMP considered that this new excipient did not constitute a major safety issue.

Overall, the CHMP was of the opinion that the observed safety data presented with this application for nepafenac 3 mg/ml were in general reassuring as the resulting safety profile was largely in line with the known profile of nepafenac 1 mg/ml. No differences in the adverse events that lead to discontinuations have been observed.

The majority of adverse events were local ocular adverse events and were characteristic of those observed with other NSAIDs. However, some adverse events such as corneal oedema, conjunctival haemorrhage, increased intraocular pressure, headache, and arterial hypertension were reported with a slightly higher incidence and some events such as corneal epithelial microcysts and retinal haemorrhage were reported as new events in nepafenac 3 mg/ml QD group compared to nepafenac 1 mg/ml TID group.

Concerns about corneal oedema were resolved following additional clarification from the MAH as this event was considered likely related to the surgery procedure and cases were generally reported as nonserious, not related to study drug and reversible which is reassuring. Furthermore, as no difference in the incidence of increased intraocular pressure was observed at day 14, the CHMP considered this issue to be resolved.

As NSAIDs are known to produce ocular bleeding, the CHMP concluded that an increased potential for ocular haemorrhage was plausible for the new formulation which provides for a higher strength (3 mg/ml) than the one authorised (1 mg/ml). The CHMP however considered that the existing warning in section 4.4 of the SmPC in relation to ocular bleeding was adequate to address this concern. Furthermore, the risk management plan already includes a potential risk in this respect.

For the ADRs headache and arterial hypertension, the CHMP was of the opinion that a causal relationship to the use nepafenac 3 mg/ml could not be excluded and therefore recommended the addition of these ADRs in SmPC section 4.8. A corresponding update should be performed for the already approved 1 mg/ml formulation.

The lack of drug interaction studies, was considered justified by the CHMP taking into account the low systemic exposure to nepafenac in humans, and also that no drug interactions were reported in any clinical study involving nepafenac 3 mg/ml and post-marketing data involving nepafenac 1 mg/ml eye drops.

No new safety issue arose from post-marketing safety data for nepafenac 1 mg/ml. An unexpectedly high number of reports of visual acuity reduced were noted by the CHMP, but the majority of these cases were considered to be related to an underlying ocular condition (such as eye infection, increased intraocular pressure, etc.) rather than being caused by nepafenac.

During the assessment, the CHMP also raised concerns over potential medication errors of the approved 1 mg/ml and new proposed 3 mg/ml formulation due to the different posologies as well as the potential for off-label use of the new formulation. However, the inclusion of the statement "once daily" in the labelling was considered appropriate by the CHMP to address the concern of medication errors. Furthermore, the CHMP agreed with the inclusion of a warning in section 4.4 of the SmPC to prevent use of the 3 mg/ml formulation for the reduction in the risk of postoperative macular oedema, which is the second approved indication for nepafenac 1 mg/ml. The CHMP also recommended updates to the RMP (see section 2.7. for details).

From the safety database all the adverse reactions reported in clinical trials have been included in

the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the CHMP was of the opinion that the observed safety data presented with this application for nepafenac 3 mg/ml were in general reassuring as the resulting safety profile was largely in line with the known profile of nepafenac 1 mg/ml. The product information for nepafenac 3 mg/ml was considered to adequately address all safety concerns.

2.7. Pharmacovigilance

Risk Management Plan

The MAH provided a new version of the RMP with this application.

In this new version, the exposure in patients with nepafenac has been updated with the data from the additional clinical trials. Other relevant sections of the safety specifications, Pharmacovigilance Plan and other chapters were updated as well to reflect the latest information. No new safety concern has been identified. However, the section on medication errors has been updated to describe the risk associated with the different posologies of nepafenac 1 mg/ml and 3 mg/ml and to reflect the measures taken to minimise this risk

The CHMP agreed in general with the update of the RMP. However, in addition to a number of minor comments which were all implemented during the assessment, the CHMP recommended the update of the safety concern for off-label use as the new formulation is only proposed for prevention and treatment of postoperative pain and inflammation, while nepafenac 1 mg/ml has also been approved for the reduction of the risk of macula oedema following cataract surgery. Finally, the section on the potential for overdose was updated in response to a request from the CHMP to reflect the potential medication error of using nepafenac 3 mg/ml three times a day.

The summary of the EU-RMP is as follows:

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Corneal disorders (identified): -Delayed corneal healing -Corneal melt -Corneal ulceration	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC adequately addresses this risk: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of NEVANAC and should be monitored closely for corneal health.* *Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if NEVANAC is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below. *Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse reactions which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions.* In Section 4.8 (Undesirable effects) of the SmPC the following corneal adverse reactions are stated: *Uncommon: keratitis, punctate keratitis, corneal deposits* *Not known: impaired healing (cornea), corneal epithelium defect, corneal opacity, corneal scar* In section 4.8 (Undesirable effects) of the SmPC for NEVANAC 1 mg/ml, the following corneal adverse reactions observed in diabetic patients exposed to NEVANAC for 60 days or greater for the prevention of macular oedema post cataract surgery are stated: *Common: punctate keratitis* *Uncommon: corneal epithelium defect* In addition, *Patients with evidence of corneal epithelial breakdown should immediately discontinue use of NEVANAC and should be monitored closely for corneal health (see section 4.4).*
Off label use (identified)	• routine pharmacovigilance • in order to better characterize, evaluate and subsequently minimize this risk a DUS will be performed subsequent to approval of the new indication, when the product is on the market with the new indication for a minimum of 6 months. This	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC and the PIL clearly indicate which population the product is authorized for. The appropriate treatment duration and risks for off label use are also indicated in the warning section.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	study will be conducted in the network of databases from the National Health Databases in Denmark and the PHARMO Record Linkage System database (PHARMO-RLS) of the PHARMO Institute for Drug Outcomes Research in the Netherlands. This will be a cohort study of users of nepafenac and users of other selected ophthalmic NSAIDs. An overview of the study protocol for this DUS is presented in Section I.2.4.	In order to prevent the use of NEVANAC 3 mg/ml for reducing the risk of postoperative macular oedema associated with cataract surgery, the following statement is to be added in Section 4.4 (Special warnings and precautions for use) of the SmPC: *NEVANAC 3 mg/ml eye drops, suspension should not be used for the reduction in the risk of postoperative macular oedema associated with cataract surgery as efficacy and safety of this strength for this indication has not been studied.*
Increased ocular bleeding (potential)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC adequately addresses this risk: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. NEVANAC should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.*
Potential of medication errors (potential)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC and the PIL clearly indicate which population the product is authorized for. The posology and appropriate treatment duration are also indicated in the product information. In order to help to differentiate the 2 strengths of NEVANAC (1 mg/ml and 3 mg/ml) and therefore, mitigate the potential risk for inadvertent substitution of the two products, Alcon is adding 'once daily' on the carton for NEVANAC 3 mg/ml.
Interaction with anti-inflammatory steroids (potential)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC adequately addresses this risk: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if NEVANAC is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.
Additive effect with BAK (potential)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC adequately addresses this risk: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since NEVANAC contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.*
Interaction with medicinal product which may prolong bleeding time (potential)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC adequately addresses this risk: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. NEVANAC should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.*
Long term use of NEVANAC (missing information)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. The SmPC is clearly indicating the maximal treatment duration, as well as the potential risks and actions to be exercised with frequent or prolonged use of NEVANAC: Section 4.4 (Special warnings and precautions for use) of the SmPC states: *Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since NEVANAC contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.* Additionally, a warning is included regarding the use of NEVANAC in patients with concurrent ocular diseases for whom the

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		risk for corneal adverse reactions may increase with the prolonged use.
Use in patients with concurrent ocular diseases (missing information)	• routine pharmacovigilance • no additional activity is proposed at this time	No additional risk minimisation activities beyond the appropriate identification in the product information are needed. In Section 4.4 warning is included regarding the use of NEVANAC in patients with concurrent ocular diseases since these patients may be at increased risk for corneal adverse reactions which may become sight threatening. The risk for these corneal adverse reactions may increase with the prolonged use (see missing information above).
Use in patients using topical ocular medications (missing information)	• routine pharmacovigilance • no additional activity is proposed at this time	The following information is included in the SmPC in relation with the concomitant use of NEVANAC with other topical medicinal products with potential interaction/additive effect: *Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if NEVANAC is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.* *There are very limited data on the concomitant use of prostaglandin analogues and NEVANAC. Considering their mechanism of action, the concomitant use of these medicinal products is not recommended.*

2.8. User consultation

The applicant has submitted an addendum to the initial user testing report addressing some minor differences between the tested package leaflet (Nevanac 1 mg/ml, eye drops) and the package leaflet for the 3 mg/ml presentation. In addition, a justification for not performing additional testing for Nevanac 3 mg/ml has been included. Since the package leaflets have minor differences with little impact on readability, the submitted documents can be considered acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The MAH has applied for a new formulation of nepafenac, eye drops, suspension, including an increased concentration of the active ingredient (3 mg/ml), using a smaller particle size of

nepafenac and enhancing the viscosity using a carbopol-guar vehicle. The new formulation was claimed by the MAH to increase convenience and compliance by patients as it is intended for once daily use only.

In the pivotal and supportive clinical trials C-09-055 and C-11-003, there was a statistically significant and clinically relevant anti-inflammatory effect shown for nepafenac 3 mg/ml eye drops, suspension, applied once daily (QD) during a 14 days investigation period post cataract surgery. The effect was demonstrated by superiority over placebo (C-09-055 and C-11-003) and non-inferiority compared to nepafenac 1 mg/ml eye drops, suspension used three times daily (TID) (C-09-055) based on the percentage of patients cured, which was defined as a composite endpoint of absence of inflammation signs.

Furthermore, no relevant differences between treatments were observed with regards to pain resolution, as determined by the rate of pain-free patients at day 14 after surgery, when nepafenac 3 mg/ml QD was compared to nepafenac 1 mg/ml TID and nepafenac 3 mg/ml was also superior to its vehicle in this respect.

Therefore, the CHMP considered that both formulations and related posologies render similar anti-inflammatory and pain control effects during the postoperative period after cataract extraction.

Uncertainty in the knowledge about the beneficial effects.

Nepafenac was initiated the day prior to surgery and continued on the day of surgery and for 14 days thereafter. Like for the approved nepafenac 1 mg/ml formulation, treatment duration up to 21 days was proposed by the MAH in the product information for nepafenac 3 mg/ml. However, only a small number of patients remained on treatment up to 21 days with the current formulation. Since the recommended treatment duration is for short-term, the CHMP concluded that the proposal would nevertheless be acceptable, provided a cross reference is included in section 4.2 of the SmPC referring physicians to SmPC section 5.1 which informs about the limited available data.

Furthermore, the Committee noted that there was information lacking on the potential effect of carbopol-guar used as vehicle in the new nepafenac 3 mg/ml formulation with regards to the global effect of this formulation.

The CHMP also expressed concerns about the high discontinuation rate in the vehicle study arms and the potential impact on the study results. However, similar results were achieved in previous studies. In addition, the majority of discontinuations were due to treatment failures and therefore the CHMP considered that the imbalance in the discontinuation rate was likely being indicative of the efficacy of nepafenac 1 mg/ml and 3 mg/ml.

Risks

Unfavourable effects

Overall, the safety profile of nepafenac 3 mg/ml, eye drops, QD was considered by the CHMP to be reassuring since it was generally in line with that for nepafenac 1 mg/ml TID.

The majority of adverse events reported in the context of the clinical trials were local ocular adverse events and were characteristic of those observed with other NSAIDs. The CHMP expressed concerns in relation to a higher risk of ocular bleedings related to the higher exposure to the active ingredient after application of nepafenac 3 mg/ml as compared to the current 1 mg/ml formulation and the potential of adverse drug reactions of headache and arterial hypertension. The latter were added to SmPC section 4.8, while the risk of ocular bleedings was considered adequately addressed by a warning in SmPC section 4.4.

Uncertainty in the knowledge about the unfavourable effects

Some uncertainties were detected following safety assessment of nepafenac 3 mg/ml. The limited data for exposure beyond 16 days and up to 21 days of treatment was noted by the CHMP. However, as has been discussed in the context of the efficacy data, the CHMP concluded that the available data were sufficient to support a recommendation of short term treatment over 3 weeks after surgery. Long-term safety, however, remains an issue of concern and is addressed in the EU-RMP.

Furthermore, the carbopol guar excipient was considered an uncertainty by CHMP as limited information was available. However, since the overall safety profiles of the new formulation and the approved 1 mg/ml formulation were comparable, the CHMP did not consider it to be a major issue.

In addition, the CHMP raised concerns over potential medication errors as the new 3 mg/ml formulation should be applied once daily while the approved 1 mg/ml formulation is to be used three times a day. Therefore, the CHMP recommended that measures be taken to reduce the risk of over- and underdosing and agreed to the inclusion of the statement "once daily" in the labelling of nepafenac 3 mg/ml.

There was also uncertainty about potential off-label use of the new formulation for the reduction of the risk of postsurgical macula oedema following cataract extraction. The CHMP agreed that a warning should be included in section 4.4 of the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

This new formulation would, in principle, be more convenient for the patients as it is given once instead three times daily. This can be considered a relevant advantage in particular as comparable efficacy has been demonstrated for the prevention and treatment of pain and inflammation post cataract surgery for the new formulation with regards to the existing 1 mg/ml eye drops.

A slightly higher risk of ocular bleedings as well as headache and arterial hypertension has been observed, and there were concerns over potential medication errors and off-label use. However, these risks were considered by the CHMP to be manageable and adequately addressed in the final product information and the RMP.

The proposed formulation contains a carbopol-guar vehicle to enhance ocular retention. So far guar excipient has never been used in an ophthalmic medicinal product and therefore, the potential impact on the safety and efficacy profile of nepafenac 3 mg/ml is unknown. The CHMP considered that additional information from post-marketing should help to fill this gap.

Benefit-risk balance

The CHMP considered that the overall benefit-risk profile of nepafenac 3 mg/ml is positive.

Discussion on the benefit-risk balance

Overall, the CHMP was of the opinion that efficacy and safety of the new nepafenac 3 mg/ml formulation (QD) has been adequately demonstrated for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery. The CHMP considered that the benefits of the anti-inflammatory and analgesic effect of nepafenac 3 mg/ml outweigh the minor safety concerns identified for the new formulation compared to the existing 1 mg/ml strength. Concerns of potential medication errors and off-label use have been sufficiently addressed in the safety information.

3.1.1.1. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Nevanac 3 mg/ml in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

The active substance is not a new active substance.