

SCIENTIFIC DISCUSSION

1. Introduction

A cataract is opacity of the lens of the eye that causes partial or total blindness. The major advances in the surgical treatment of cataract in the last century have not been matched by advances in the understanding of cataract formation, in approaches to prevention, or in nonsurgical therapy. Fifty percent of blindness globally is estimated to be caused by cataract, accounting for 15 million blind individuals. The vast majority of cataract extractions are for acquired cataract, with senile or age-related cataract predominating.

The only treatment for cataract is to surgically remove the opacified lens from the eye to restore transparency of the visual axis. Surgery currently is indicated if symptoms from the cataract interfere with the patient's ability to meet his or her needs of daily living; there are no criteria based upon the level of visual acuity per se.

Two techniques are currently used for cataract extraction: Standard extracapsular cataract extraction, which typically involves removal of the lens nucleus in one piece and phacoemulsification, also called small incision surgery, in which the lens is fragmented using ultrasound energy

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 edema.

Although cataract surgery has become less traumatic in the past decade with advances in surgical technique, the treatment of ocular pain and inflammation is still a necessity. Anti-inflammatory therapies are administered to reduce postoperative inflammation [including corneal edema, iritis (aqueous cells and flare)] and to help prevent the posterior segment complication of cystoid macular edema. While corticosteroids are very effective in controlling inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) provide surgeons with an alternative therapy for the reduction of inflammation associated with cataract surgery 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 and Indomethacin 1 mg/ml.

Nepafenac is a member of the nonsteroidal anti-inflammatory drug (NSAID) class. The drug is formulated as a suspension applied by the topical ocular route, and is intended for the prevention and treatment of pain and inflammation associated with cataract surgery. Nepafenac (amfenac amide) is a prodrug which is converted to amfenac by intraocular hydrolases. Amfenac inhibits both cyclooxygenase COX-1 and COX-2 activity.

To benefit from the mechanism of action of nepafenac (i.e., inhibition of the cyclooxygenase enzyme), the suppression of inflammation should be most effectively achieved if therapeutic levels of the drug are present in the tissue at the time of surgical insult. Therefore, the proposed dosing regimen for nepafenac 1 mg/ml Eye Drops, Suspension begins one day preoperatively and continues on the day of surgery and for up to 3 weeks of the postoperative period.

The applicant submitted a complete independent application according to Article 8.3 of Directive 2001/83/EC, as amended.

The indication and posology proposed by the applicant for NEVANAC was for the '*Prevention and treatment of pain and inflammation associated with cataract surgery.*'

The dose is one drop in the affected eye(s) three times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and for up to 3 weeks of the postoperative period.

2. Quality aspects

Introduction

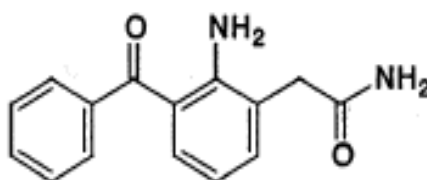
NEVANAC is formulated as a sterile, preserved, multi-dose aqueous suspension for topical ophthalmic application (eye drops), containing 1 mg of nepafenac (active substance) per ml (0.1 %). Nepafenac is an anti-inflammatory prodrug which is converted to amfenac by intraocular hydrolases. Excipients used in preparation of NEVANAC are those typically used in ophthalmic formulations. It contains benzalkonium chloride as a preservative, disodium edetate as a preservative aid and chelating agent, sodium chloride and mannitol as a tonicity agents, tyloxapol as a wetting agent, carbomer as a suspending agent and purified water as a vehicle. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

NEVANAC is light yellow to dark yellow uniform suspension. It is packaged in 8 ml bottles made with low-density polyethylene (LDPE). The bottle is equipped with a plastic dispensing plug made of low density polyethylene (LDPE) and plastic closure made of white polypropylene (PP).

Active Substance

Nepafenac is chemically designated as 2-(2-Amino-3-benzoylphenyl) acetamide or 2-Amino-3-benzoylbenzeneacetamide. The structure of nepafenac is shown in figure 1.

Figure 1: Chemical structure of nepafenac



Nepafenac is yellow crystalline or powdery substance practically insoluble in water. An aqueous suspension at 0.1 % gives an average pH of 6.75. The coefficient partition n-octanol/water is 128. This substance melts at approximately 185 °C and it does not show polymorphism. Nepafenac is an achiral substance and there are no possible variations in the stereochemical configuration.

- **Manufacture**

Information about the manufacturing process has been provided using an ASMF procedure. A three-step synthesis followed by a final crystallization has been well described, critical parameters and accompanying in-process controls have been defined. Possible impurities, including their origin and the main degradation pathways, have been characterized. Appropriate specifications and limits have been established for residual solvents. No metal catalysts are used during the manufacture and therefore a standard pharmacopoeial limit and method was proposed.

Confirmation of the chemical structure of nepafenac was provided by elemental analysis (confirmation of the determined elementary composition) and spectroscopic methods as UV, FT-IR, ¹H-NMR and ¹³C-NMR, 2D-NMR (2D-COSY and 2D-HETCOR), MS (EI and CI) and X-ray powder diffraction. The assessment of possible polymorphism has been performed by re-crystallisation of the drug substance in various solvents of different polarities and at different rates. Although re-crystallisation

resulted in material of various appearance, there was no evidence of the formation of polymorphic forms of nepafenac.

Since the formulated product is aseptically prepared using gamma irradiated drug substance a few batches of gamma irradiated nepafenac were stored for 1 year, but showed no evidence of polymorphism.

- **Specification**

The drug substance specification includes tests for physical appearance, colour and clarity of the solution, identification (IR and HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), loss on drying, heavy metals, sulphated ash and bioburden.

The proposed analytical methods have been validated with regard to relevant guidelines and include specificity, repeatability, linearity and precision, limit of quantification, accuracy and robustness as appropriate. No validation was performed for the methods described in the Ph. Eur. In general, analytical methods proposed are suitable to control the quality of the drug substance.

Data was provided on 5 batches of nepafenac all of which were manufactured using the commercial route. All the batches complied with the requirements in the drug substance specification.

- **Stability**

Stability studies have been performed on 5 batches of the drug substance. Data was provided for batches stored up to 52 months at 25 °C/60 % RH (long term storage conditions) and for batches stored for 6 months at 40 °C/75 % RH (accelerated conditions). Additionally, data from photostability study (UV irradiation) and from short-term stressed degradation studies (including exposure to heat, acid and base degradation, oxidative and reductive conditions) was provided. The stability of the drug substance exposed to gamma irradiation has also been studied. The data showed that gamma irradiated nepafenac meets the requirements of the drug substance specification and no changes in the impurity profile or in the crystalline form were observed.

The stability studies demonstrated that the drug substance is stable and confirmed the proposed re-test period.

Medicinal Product

- **Pharmaceutical Development**

The objective of the pharmaceutical development was to develop a stable, well-preserved sterile suspension. Suspension was developed due to the poor aqueous solubility of the drug substance. NEVANAC is formulated as an isotonic aqueous suspension with physiological pH. The choice and function of the excipients in the formulation has been adequately described and justified. Benzalkonium chloride was used as a preservative agent because it is a broad spectrum antimicrobial preservative which has been successfully used in topical ophthalmic formulations. The efficacy of the selected preservative system even at the lower limit concentrations of the shelf-life specifications has been demonstrated. Carbomer, a viscosity modifying agent, was used in order to facilitate the suspension of nepafenac particles. The concentration of this agent was based on the results from pre-clinical corneal penetration study. Other excipients chosen for the formulations are: disodium edetate as a preservative aid and chelating agent, sodium chloride and mannitol as a tonicity agents, tyloxapol as a wetting agent and purified water as a vehicle. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

During the development a key physiochemical characteristics relevant for the product performance (particle size, polymorphism and uniformity/homogeneity of dose) have been identified and analysed. The proposed manufacturing process ensures uniform particle size in the suspension. The results of extensive studies on polymorphism proved that that the formation of polymorphs in the suspension is

not likely to occur. NEVANAC has been developed to be a homogeneous suspension which shows minimal sedimentation and is easily resuspendable. The resuspendability has been evaluated and it was proven that the product is resuspended within five seconds. The homogeneity of the suspension and uniform content of nepafenac within a batch and within each drop has been studied and proven.

The choice of sterilisation method has been justified. In the proposed sterilisation method the drug substance is gamma sterilised prior to aseptic addition of milling slurry. Terminal sterilisation was considered but was not possible because of the heat liability of the primary packaging. Steam sterilisation of the final bulk suspension could not be used because the nepafenac drug substance is heat sensitive.

- Adventitious Agents

None of the excipients used in the formulation of the drug product are of human or animal origin.

- Manufacture of the Product

The manufacturing process is composed of five major steps:

- 1) Preparation of milling slurry: transfer of tyloxapol solution to milling tank, addition of beads and steam sterilisation followed by aseptic addition of gamma sterilised drug substance and aseptic ball milling.
- 2) Preparation of the vehicle concentrate (containing soluble ingredients) and carbomer slurry followed by pH adjustment and bulk sterilisation.
- 3) Aseptic separation of the milling slurry from the beads, addition of the slurry to the reactor with the vehicle concentrate followed by rinsing of the beads and bringing the batch to the final weight.
- 4) Sterile filling of a sterile suspension to previously sterilised packaging components (ethylene oxide).
- 5) Secondary packaging.

Critical steps of the manufacturing process have been identified and are sufficiently controlled by in-process control testing. The used in-process controls are considered satisfactory to guarantee the drug product of an appropriate quality.

The manufacturing process has been validated using three commercial scale batches manufactured at the commercial manufacturing site. All critical steps of the process were covered by validation studies.

Batch analysis data indicate satisfactory uniformity and compliance with the proposed specifications.

- Product Specification

The finished product specifications include test for appearance, drug substance identification (HPLC and TLC), drug substance assay (HPLC), impurities (HPLC), benzalkonium chloride identification and assay (HPLC), disodium edentate identification and assay (HPLC), pH, particle size (HIAC), osmolality, resuspendability, viscosity, fill volume, sterility.

All methods used for testing the drug product have been satisfactorily validated. The HPLC methods have been validated for accuracy, precision, specificity, linearity, range, robustness, limit of detection and quantitation. A light obscuration method utilising a commercial HIAC instrument used for the determination of particle size has also been validated. Validation for methods described in Ph. Eur. was deemed to be unnecessary. Selected analytical methods and proposed limits for a release and stability testing of the drug product are considered appropriate for control of an ophthalmic product.

- **Stability of the Product**

Stability data for three commercial scale batches of the drug product stored at 25 °C/40 %RH and 30 °C/65 %RH up to 78 weeks have been provided. In addition stability data from accelerated 40 °C/NMT 25 %RH, intermediated 4 °C/35 %RH, photo-stability and freeze-thaw cycle studies were provided. The overall stability data showed that NEVANAC is chemically, physically and microbiologically stable.

In-use stability study has been performed on two commercial scale batches. The provided in-use stability data supported proposed 28-day in-use period.

In summary, the stability results support the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are appropriate for an ophthalmic preparation. The results of the tests indicate that the active substance and the finished product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve this as Follow-Up Measure after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

Pharmacology

- **Primary pharmacodynamics**

Nepafenac is a non-steroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

In vitro and *in vivo* studies were conducted to characterize anti-inflammatory activity of nepafenac. Nepafenac, the carboxamide analog of 2-amino-3-benzoylbenzeneacetic acid, is the prodrug form of the above mentioned nonsteroidal anti-inflammatory drug, amfenac, and is as such an intrinsically weak inhibitor of cyclooxygenase (prostaglandin H synthase). However, its active metabolite, amfenac, results in a high inhibition of cyclooxygenase activity. Both nepafenac and amfenac are slightly less potent than diclofenac, but show the same preference of COX-1 to COX-2.

As an uncharged prodrug, nepafenac exhibits high rates of corneal penetration *in vitro*, readily providing intraocular hydrolases with drug-substrate for the formation of the active metabolite, amfenac. The high suppression of cyclooxygenase is attributable to a time-dependent, irreversible inactivation of the enzyme. While this inactivation is irreversible, the creation of new functional enzyme is not suppressed. Therefore, the reduction of enzyme concentration is not itself permanent and thus does not adversely affect long-term cellular responses. The lipoxygenase pathway and occurrence of possible adverse effects mediated by lipoxygenase derived mediators (leukotrienes) has not been investigated. However, it is not a major concern taking into account the short duration of treatment.

Rates of *in vitro* bioactivation of nepafenac are in the order of retina/choroid > iris/ciliary > cornea. Following a single topical ocular dose, nepafenac distributes locally both to the iris/ciliary body and

retina/choroid where, upon bioactivation (hydrolysis), it effectively suppresses *ex vivo* prostaglandin synthesis. Sustained suppression of prostaglandin synthesis is seen for a period of more than 6 hours in the iris/ciliary body. Similar inhibitory effects, although slightly lower in magnitude, are observed *ex vivo* in tissue of the retina/choroid. As a consequence of its ocular biodistribution and bioactivation by intraocular tissues, a single topical prophylactic dose of nepafenac effectively inhibits trauma-induced aqueous humor PGE₂ accumulation and concomitant breakdown of the blood aqueous barrier *in vivo*, with a maximum efficacy (60% inhibition) described with a single administration of a 0.3 mg/ml formulation of nepafenac that is maintained throughout the highest concentration tested (3 mg/ml). Assessment of the duration of suppression of protein accumulation in the aqueous humor following a single topical ocular dose of nepafenac 1 mg/ml revealed an immediate suppression of vascular leakage that was sustained for a duration of at least 8 hours. While Diclofenac 1 mg/ml inhibited the vascular permeability response for 4 hours post-dosing, but failed to do so at the 8 hour time-point. Drug efficacy is also observed in a more stringent Concanavalin A-induced panretinal inflammation model where topical nepafenac administration leads to significant reductions in retinal edema and blood-aqueous and blood-retinal barrier leakage.

- Secondary pharmacodynamics

Secondary pharmacology studies evaluated the ability of nepafenac to suppress retinal neovascularization. These included *in vitro* assessments of VEGF-induced tube formation of human and bovine retinal microvascular endothelial cells cultured in a vitronectin/fibronectin/laminin gel. In these studies, amfenac, the active metabolite of nepafenac, effectively inhibited tube formation.

The *in vitro* work was accompanied by *in vivo* evaluations of the efficacy of topically dosed nepafenac in several animal models of neovascularization and diabetic retinopathy. The administration of 1 mg/ml nepafenac four times a day, resulted in a significant suppression (55%) of preretinal neovascularization when compared to vehicle treatment in a rat model of oxygen-induced retinopathy. A transgenic mouse model of VEGF overexpression found that 1 mg/ml nepafenac caused a reduction (43%) in retinal neovascularization. Several studies examined the effect of 0.3–5 mg/ml nepafenac on laser-induced choroidal neovascularization (CNV) and found a dose-dependent inhibition of CNV of up to 78%. Nepafenac 5 mg/ml caused a qualitative decrease in choroidal endothelial cell proliferation in a rabbit model of lipid peroxide induced CNV.

A separate study assessed the ability of nepafenac (3 mg/ml) to inhibit VEGF-induced retinal vascular permeability in the rabbit. When administered four-times-daily, nepafenac (3 mg/ml) was ineffective in preventing VEGF-induced retinal vascular leakage.

In a rat model of streptozotocin-induced diabetes, nepafenac produced significant reduction in retinal leukostasis, PGE₂, and superoxide formation, as well as TUNEL-positive capillary cells, acellular capillaries, pericyte ghosts, and oscillatory potential changes; while showing no significant effect on VEGF expression, or the hyperglycemic state of diabetic and nondiabetic control.

From the acute safety pharmacology study it can be concluded that nepafenac does not show anaesthetic properties after application at a single dose level. Although a direct analysis of the anaesthetic properties of nepafenac was not completed in the preclinical safety evaluations, known adverse effects of chronic exposure to anaesthetic drugs such as corneal opacity, queratitis or delayed wound healing or epithelial defects following corneal incision, were not observed in the repeat dose topical ocular studies. A recent publication investigated the anaesthetic properties of nepafenac and other NSAIDs in cats and in cultured mice trigeminal ganglion neurons concluded that nepafenac inhibited the polymodal nociceptor activity in cat corneas; however, it did not significantly suppress sodium currents in the mice trigeminal ganglion neurons, demonstrating that nepafenac does not exhibit local anaesthetic effects.

- Safety pharmacology programme

Safety pharmacology studies investigated the effects of nepafenac on the central and autonomic nervous, cardiovascular, pulmonary, gastrointestinal, metabolic and renal systems. *In vitro* studies at 1, 10 and 100 µM concentrations of nepafenac did not interact with 21 different receptors and binding

sites including steroid receptors, and 1 μ M and 10 μ M concentrations had no (statistically) significant effect on guinea pig ileum (smooth muscle) responses to acetylcholine, histamine and barium chloride.

In vivo studies showed that nepafenac (3 mg/kg) had no effect on general behaviour, body temperature, or electroshock-induced convulsions. At the same concentration, nepafenac produced a statistically significant increase in barbiturate-induced sleep time. However, the increase was not considered to be clinically meaningful.

The active metabolite of nepafenac, amfenac, had no effect on the HERG tail current (a measure of cardiac repolarization) at concentrations up to 100 ng/ml. Three mg/kg of nepafenac had no statistically significant effect on phenylquinone-induced writhing and 1 mg/kg administered subcutaneously had no statistically or biologically relevant effects on pulmonary or cardiovascular functions including the lead II ECG. Likewise, the sodium salt of amfenac at 1.08 mg/kg IV (cumulative dose 1.55 mg/kg) had no effect on blood pressure, heart rate or lead II ECG, including QTc interval, in anesthetized dogs. Nepafenac (0.1 to 3 mg/kg) also did not significantly affect gastrointestinal motility, urine output, pH or electrolyte concentrations. Oral doses of 3 mg/kg showed no gastric ulcer potential and topical ocular doses up to 500 μ g showed no anaesthetic activity in rabbits. These data suggest that nepafenac 1 mg/ml Eye Drops, Suspension will not exhibit a significant side effect potential if administered as proposed.

The effect of NEVANAC on electroretinogram (ERG) (photopic and scotopic) was studied in a 9-month repeat-dose topical ocular safety study in New Zealand F1 cross pigmented rabbits. No adverse effects were observed from the provided data.

- Pharmacodynamic drug interactions

No nonclinical pharmacodynamic drug interaction studies were conducted with nepafenac or amfenac. The low systemic exposure following topical ocular administration of nepafenac and its pharmacology make significant drug interactions unlikely. Additionally, topical ocular NSAIDs should be used with caution in patients who are receiving other medications which prolong bleeding time or in patients with known bleeding tendencies or patients with a known history of peptic ulceration.

Although the applicant has not conducted pharmacodynamic interaction studies, the lack of such data could be considered justified taking into account the low systemic exposure to nepafenac in humans, and also that no drug interactions were reported so far in any clinical study involving nepafenac 1 mg/ml Eye Drops.

Pharmacokinetics

- Methods

In the non-clinical studies, amfenac amide and its hydrolysis product, amfenac, were determined in plasma by HPLC/tandem mass spectrometry (HPLC/MS/MS). The method of analysis, validated in plasma from rats, rabbits and cynomolgus monkeys, demonstrated for both analytes in the three matrixes fully adequate accuracy, precision, specificity and stability for routine analysis of GLP study samples, with detection limits between 0.025 to 75 ng/mL.

In single dose absorption studies there was no indication of GLP fulfilment.

- Absorption and bioavailability

All studies following a single dose were performed only in males, so it was not possible to compare sex differences in pharmacokinetic parameters. However, toxicokinetic studies (repeated doses) were performed in both sexes and no significant differences between males and females were observed. Amfenac amide is hydrolysed to amfenac *in vivo*. Studies in rats, rabbits and monkeys utilizing different routes of administration (intravenous, oral, topical ocular) showed that plasma concentrations of amfenac amide and amfenac declined with half-lives of less than one hour. However the terminal elimination phase could not be captured due to low assay sensitivity in these experiments. Plasma half-lives of total radioactivity were longer than amfenac amide and amfenac ranging from 20 hours in rats to 50 hours in monkeys. Although the plasma half-lives of total radioactivity were longer, initial

plasma radioactivity concentration declined rapidly. The radioactivity in the terminal phase may be due to the presence of minority metabolites.

The absolute oral bioavailability of amfenac amide in rats is low, approximately 6%, and it could be due to first pass metabolism; however, the possibility of enterohepatic recycling had not been investigated. The percentage of the dose reaching the systemic circulation as amfenac is substantially higher. The percentage of a radiolabeled dose of amfenac amide absorbed is substantially higher at approximately 85%.

Following the topical ocular dose in male rabbits, the higher amfenac concentration may be due to enzymatic hydrolysis of amfenac amide to amfenac. Based on AUC_{0-inf} , the ratio of amfenac to amfenac amide was approximately 10:1. The systemic bioavailability (%F) of amfenac amide by topical ocular dosing route was high.

In repeated dose studies amfenac amide was topically administered to rabbits for a period of 6 months, to cynomolgus monkeys for a period of 3 months, and orally administered to rats and for a period of 6 months. The plasma AUC or C_{max} remained constant during the time, indicating a non cumulative process of elimination. In addition, these parameters showed no differences regarding sex. Increasing the dose produced a proportional increment in C_{max} and AUC in rabbits, monkeys and rats.

Based on studies provided pregnancy seemed not to influence the absorption of the Amfenac Amide.

▪ Distribution

With respect to distribution in ocular tissues following the single 30 ng topical ocular dose of amfenac amide, plasma concentrations of amfenac amide and amfenac were low (2 and 6 ng/lm, respectively). Highest concentrations of both were observed in tissues associated with the site of dosing (conjunctive and cornea). Both amfenac amide and amfenac tissue concentrations generally declined in a biphasic manner. Level of exposure in conjunctiva and cornea (AUC_{0-8h}) for amfenac were 3.5 and 4 fold higher than those for amfenac amide. The radioactivity was absorbed into the eye following a topical ocular dose of a 0.3% ^{14}C -amfenac amide to the New Zealand white rabbits and Dutch Belted rabbits and distributed to posterior ocular tissues by local distribution of the drug. The results showed that amfenac amide and its metabolites, *probably* did not bind to melanin pigmented tissues.

Distribution in tissues was investigated in male rats after oral dose of ^{14}C amfenac amide. C_{max} was reached at 0.5h for most tissues following single or multiple oral dose, indicating rapid absorption under both dose regimens. Accumulation of ^{14}C -amfenac amide was evident in all tissues following 14 daily oral doses (and for majority of tissues for single dose), indicated by concentration ratios (multiple dose:single dose) and relative AUC_{0-last} . Elimination half –lives following multiple dosing were generally higher than after a single dose, and tissue half lives were longer than plasma half-lives. The observed plasma radioactivity half lives following single and multiple doses were longer than the half-life observed in the pharmacokinetic study following oral administration of 3 mg/kg ^{14}C - amfenac amide to male rats.

Oral administration of ^{14}C - amfenac amide to rat dams on day 12 and 18 of gestation resulted in distribution of radioactivity to maternal tissues and placental transfer of radioactivity into the developing fetus. Absorption and distribution of radioactivity to maternal tissues occurred rapidly ($T_{max}=0.5h$). Since samples were only collected up to 24 hours, tissue half –lives may be underestimated.

Radioactive drug equivalents were secreted into milk following oral administration. Milk:plasma ratios were less than unity and levels of radioactivity in milk and plasma declined with similar half-lives.

^{14}C - amfenec amide binds with high affinity (72-84%) to plasma proteins of rat, monkey and human *in vitro* in a concentration independent manner over the concentration range 10 to 1000 ng/mL. The extent of plasma protein binding ^{14}C - amfenac amide between these species was similar.

- **Metabolism**

In the eye amfenac amide is hydrolysed to its pharmacological active form, amfenac. Amfenac amide is metabolized to amfenac and to more polar metabolites involving hydroxylations of the aromatic ring and glucuronide conjugate formation in all species tested by i.v administration (rats, monkeys and humans). The circulating plasma metabolites in human and monkey are primarily in the form of conjugates whereas those in rats are not conjugated. Metabolites observed in urine from human and monkeys are in the form of conjugates. In rats majority of metabolites in urine were not conjugated. In all species amfenac and amfenac amide in plasma were found to be non-conjugated. In humans, amfenac was the major metabolite and represented approximately 13 % of the total radioactivity in plasma. All other metabolites had percentages of less than 10%. Amfenac amide and amfenac were not observed in urine. Apart from amfenac, the most abundant human plasma metabolite has been identified as 5-hydroxy amfenac amide which represents about 9.5% of total radioactivity at C_{max} .

Incubation of ^{14}C -amfenac amide in human liver slices resulted in the formation of 12 metabolites. The major metabolite found was amfenac. Glucuronidase mediated hydrolysis showed these metabolites to be a mixture of conjugated and non-conjugated metabolites. Most part of the metabolites found in plasma or urine in all species have not been identified.

Plasma concentrations of amfenac amide and amfenac of up to at least 1000 ng/ml (approximately 3000-fold higher than the observed mean plasma C_{max} in humans (0.310 ± 0.104 ng/ml)), are not likely to elicit any clinical drug-drug interaction involving cytochrome P450-mediated metabolism of concomitantly administered drugs.

When nepafenac or amfenac was incubated with human cytochrome P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 isozymes, the only positive finding was a 36% inhibition of CYP2E1 activity at a single concentration >1000 ng/mL nepafenac. This indicates that plasma concentrations of nepafenac and amfenac up to 1,000 ng/mL, which is more than three orders of magnitude higher than the observed mean plasma C_{max} in humans (nepafenac: 0.3 ng/mL; amfenac: 0.4 ng/mL), is unlikely to elicit clinical drug-drug interactions involving cytochrome P450-mediated metabolism of concomitantly administered drugs.

Following repeated dose administrations of amfenac amide during 14 days, a statistically significant ($p<0.05$) increase in CYP4A activities (approximately 43 %) was observed in male rats. There was an apparent increase in UDPGT (*Uridine diphosphate glucuronyltransferase*) activities also in male rats. No other hepatic effects in males or females were observed.

- **Excretion**

Excretion was only examined following intravenous administration. Excretion was very rapid, with nearly 90% of the dose recovered in excreta by 24 hours post-dose. The primary route of excretion of radioactivity was via urine ($\approx 58\%$), excretion in feces was also high ($\approx 40\%$), therefore there is enterohepatic recycling.

Toxicology

The toxicology programme included single dose studies (oral route), repeat-dose studies (oral and topical) of up to 6-months duration in several species.

- **Single dose toxicity**

No single-dose toxicity study has been carried out by the topical route of administration, although it is not a major concern since topical ocular repeat-dose toxicity studies have been conducted with high doses without any significant toxicity.

Amfenac amide was systemically well tolerated in mice with an oral LD_{50} value greater than 2000 mg/kg and IP LD_{50} value greater than 1000 mg/kg for both sexes. Systemic administration of amfenac amide in rats show oral LD_{50} values greater than 100 mg/kg in males and greater than 500 mg/kg in females while when the IP route was tested, LD_{50} values were greater than 250 mg/kg in males and greater than 100mg/kg in females.

- Repeat dose toxicity (with toxicokinetics)

Oral administration

Conventional oral (gavage) repeat-dose toxicity studies were conducted in rats for a duration of 2 weeks, 3 months and 6 months, respectively. In the 2-week study, the NOAEL was 7.5 mg/kg/day based on decreases in RBC parameters. In the 3-month study, the NOAEL was 1 mg/kg/day in males based on RBC counts, and 5 mg/kg/day in females based on renal papillary necrosis. In the pivotal 6-month study, the NOAEL was 3 mg/kg/day based on reduced RBC parameters in males and increased absolute kidney and liver weights in females. In both cases findings were not accompanied by histopathological changes.

After systemic repeated administration of amfenac amide in rats, a common finding in nonsteroidal anti-inflammatory drugs is renal papillary necrosis, which appeared only in females treated at 15 mg/kg/day by gavage during 3 months. This was not observed at lower dose levels during 3 or 6 months of treatment or at higher dose levels (up to 25 mg/kg) during two weeks of treatment by the same route. Gastric irritation was not observed at any dose level in any study.

In mice adverse effects (only observed in the two-week study) such as serositis in jejunum, mesenteric lymphoid hyperplasia, EMH in spleen and liver and uterine dilatation found in treated females but not in control groups, indicated that a treatment relationship could not be entirely ruled out. However these effects appeared at elevated dose levels (25 mg/kg/day) compared to the therapeutic doses recommended in human treatment (2.4µg/kg/day).

Five repeated-dose topical ocular studies were conducted, ranging in duration from 1 to 6 months in rabbits and monkeys. Parameters evaluated on these studies included detailed pharmacotoxic observations, body weights, slit-lamp biomicroscopic ophthalmic examinations, indirect ophthalmic examinations and corneal pachymetry. Also serum chemistry and hematology evaluations, organ weights, macroscopic and microscopic pathologic evaluations were conducted in studies at 3/6 months.

Topical administration

All topical ocular repeated doses studies utilized an appropriate vehicle control group for each study. The 1-, 3-, and 6-month rabbit topical ocular studies each utilized a separate untreated control group in addition to the vehicle control group. In the 3-month monkey study the contralateral untreated eye was used as an untreated control. No significant ocular irritation or systemic toxicity following one, three or six months of daily topical ocular administration in rabbits or following three month in monkeys was observed. The NOAEL was the highest dose evaluated in each of these studies. A summary of repeated-dose topical ocular studies is tabulated below.

Table 1 Summary of repeat-dose topical ocular toxicity studies

Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL	Major findings
Rabbit NZW/both/4 by sex and dose level	0,1,3,10 mg/ml OD,QID/Topical ocular (with corneal incision)	1 month	10 mg/ml	Minimal conjunctival congestion and discharge
Rabbit NZW/both/4 by sex and dose level	0,1,3,10 mg/ml OU,QID/Topical ocular	1 month	10 mg/ml	No treatment-related findings
Rabbit NZW/both/10 by sex and dose level	0,1,3,10 mg/ml OU,QID/Topical ocular	3 month	10 mg/ml	No treatment-related findings
Rabbit NZW x NZR/both / 7 by sex and dose level	0, 3, 10 and 15 mg/ml OD,TID/Topical ocular	6 month	15 mg/ml	No treatment-related findings.
monkeys (cynomolgus) /both /4 by sex and dose level	0,1,3,10 mg/ml OD,QID/Topical ocular	3 month	10 mg/ml	No treatment-related findings

^aOD = right eye; ^bQID = four times a day; ^cTID = three times a day; ^dOU = both eyes

A low ocular irritation potential was seen in rabbits when Nepafenac suspension was administered *prior* and *subsequent* to a corneal incision. There were no postoperative ocular complications or unexpected findings in any group, and there was no evidence that *post-incision* treatment with nepafenac 1 mg/ml to 10 mg/ml resulted in ocular irritation or delayed wound healing.

Slight decreases in body weights (less than 10%) were seen in males treated at 5 and 15 mg/kg/day during 3 months but since a similar effect was not observed at 10 mg/kg/day in the 6-months study, it is not considered to be relevant.

- Genotoxicity

The standard battery for genotoxic assessment has been conducted in four studies, three *in vitro* and one *in vivo*. No evidence of mutagenic activity was observed in the bacterial reverse mutation assay and in the *in vitro* mammalian gene mutation assay. In the *in vitro* chromosome aberration assay positive results were found with and without S9 but only at dose levels where precipitation was observed with no other relation to dose. This response was not observed in the *in vivo* mouse bone marrow micronuclei test. Therefore, the risk of genotoxic potential of amfenac amide can be considered low.

- Carcinogenicity

Following a review of ICH Topic S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals, it was determined that carcinogenicity studies were not needed to support the safety of nepafenac 1 mg/ml Eye Drops Suspension based on the chemical class, short duration of therapy (up to 23 days), low systemic exposure potential, and non-clinical toxicology study results which showed no evidence of preneoplastic lesions in rats dosed daily for 6 months with up to 10 mg/kg/day of nepafenac. Furthermore, results from published information (of unknown GLP status) of available carcinogenicity data support the systemic safety of nepafenac's active metabolite, amfenac. It should be noted that the quality of information of carcinogenicity studies is very limited due to only a brief statement of results reported.

- Reproduction Toxicity

Amfenac amide was administered to male and female rats at doses of 0, 3, 10, 15 and 30 mg/kg to test fertility and early development. The dose of 30 mg/kg produced severe clinical findings and related deaths.

Table 2 **Summary of reproductive and developmental toxicity studies**

Study type	Species/ number/ sex/group	Study design	Dose levels (mg/kg/day)	Principal findings
Male fertility	Rat/25	Segment I	0, 3, 10, 15, 30	NOAEL = 10 mg/kg/day based on reduced body weight gain and sperm motility parameters
Female fertility	Rat/25	Segment I	0, 3, 10, 15, 30	NOAEL = 3 mg/kg/day based on number of viable foetuses
Embryo- foetal development	Rat/25	Segment II	0, 3, 10, 30	Maternal NOAEL = 10 mg/kg/day based on mortality Foetal NOAEL = 10 mg/kg/day based on foetal body weight and skeletal variations
	Rabbit/20	Segment II	0, 3, 10, 30	Maternal NOAEL = 3 mg/kg/day based on abortions and clinical signs suggestive of aspiration pneumonia Foetal NOAEL = 10 mg/kg/day based on external, visceral and/or skeletal malformations
Peri- and postnatal development	Rat/25	Two- generation Segment III	0, 3, 10, 15, 30	Maternal LOAEL = 3 mg/kg/day based on mortality following initiation of parturition F1 offspring NOAEL = 3 mg/kg/day based on pup viability F2 offspring NOAEL = 30 mg/kg/day

Fertility studies

The main clinical observation was yellow coloured urine that was present in a dose-related manner at all dosage levels. At the dose of 15 mg/kg, males and females showed food consumption, bodyweight and bodyweight gain depression, which was statistically significant for certain periods, but not for the whole period. The bodyweight depression was nevertheless lower than 4%. During gestation, females did not show any adverse effect on bodyweight or food consumption.

The most relevant reproductive effect was a statistically significant reduction of the sperm motility in the group receiving 15 mg/kg. In addition, sperm concentration was reduced as well; however values recorded fell into the range of the historical control data.

The fertility index decreased, especially at 15 mg/kg. Thus, the fertility index was 100%, 95.8%, 92% and 88% for 0, 3, 10 and 15 mg/kg, respectively. At caesarean, the number of viable fetuses was reduced at 10 and 15 mg/kg, while the average number of early resorptions was also decreased. Therefore, a parental/reproductive NOAEL of 3 mg/kg bw/day was selected.

With respect to the applicant's explanation on fertility parameters in males, it is agreed that the data suggest that at levels below 10 mg/kg/day or lower, effects on male reproductive effects by nepafenac in rats are not anticipated. This provides a significant safety margin given the low systemic exposure during clinical use of nepafenac 1 mg/ml Eye Drops, Suspension.

In addition organ weights were not collected during the conduct of the fertility and general reproduction study, however female organ weights in rats were taken in the 6- month rat oral dosing study; no significant changes were noted in female reproductive organ weights.

Embryo-fetal studies

The administration of amfenac amide at 3, 10 and 30 mg/kg bw/day to pregnant rats resulted to be non-teratogenic. Toxicity in the dams was manifested at 30 mg/kg, with a statistically significant

depression of the food consumption, bodyweight and bodyweight gain regarding the group of controls. At the dose of 10 mg/kg the food consumption also was decreased.

Developmental effects were evident at 30 mg/kg; the mean fetal weight decreased statistically (by 5.7% regarding controls) and also, an increased incidence of fetuses with unossified sternebrae #5 or #6, and a marginal increase in the incidence of pre-implantation loss. In addition, one 30 mg/kg/day female had nine dead fetuses, six resorptions and no viable fetuses. Therefore, the NOAEL for parental toxicity could be established in 10 mg/kg/day and NOAEL for developmental effects in 10 mg/kg/day. In a separate toxicokinetic study in pregnant rats, 10 mg/kg/day dams had mean terminal AUC-values equal to 207 ng.h/mL of nepafenac, corresponding to a safety margin in excess of 500.

The administration of amfenac amide to rabbits resulted to be less toxic compared to rats. Rabbits were provided with 0, 3, 10 and 30 mg/kg bw/day. In the 10 mg/kg group, one female aborted on GD18. At 30 mg/kg, one female was found dead on GD19, one female aborted on GD21, and one female delivered prematurely on GD29. With the exception of the female found dead, all of the above females had clinical signs prior to abortion or premature delivery including laboured breathing, decreased activity, cool to the touch, few or no faeces, soft or mucoid stools, and faecal stain in the anogenital area. The remaining doses did not show evident clinical signs as a result of the treatment.

At 30 mg/kg, the food consumption decreased slightly from day 15 to 19 and the bodyweight gain was also depressed (50% to 19% regarding controls) for day 12 to 24 of gestation. It is noted that this marginal decrease did not achieve statistical significance and animals did not show any clinical finding. Nevertheless, females dosed with 30 mg/kg showed an increased incidence of early resorptions and a statistically significant increase in the incidence of post-implantation losses. When assessed for developmental effects, it was shown that the incidence of litters with skeletal malformations and with total malformations increased at the highest dose of 30 mg/kg.

The maternal NOAEL was considered to be 3 mg/kg bw/day, while the developmental (foetal) NOAEL was 10 mg/kg bw/day. In a separate toxicokinetic study, 10 mg/kg/day dams had mean terminal AUC-values equal to 28.4 ng.h/mL of nepafenac. Based on mean steady state human $AUC_{0-\infty}$ values of 0.371 ng.h/mL for nepafenac and 1.03 ng.h/mL for amfenac, this translates into safety margins in excess of 75 and 600, respectively.

Pre-postnatal studies

The administration of amfenac amide at doses of 3, 10, 15 and 30mg/kg/day to pregnant rats from GD6 through lactation day 20 produced evident maternal and offspring toxicity in the first F1 generation but not in the second generation or F2.

The dose of 30 mg/kg produced excessive toxicity to rats, including several deaths, making difficult the assessment due to the reduced number of rats. Moreover, signs of dystocia and deaths were evident at all doses. The bodyweight of pregnant rats decreased for the gestation and lactation at the dose of 15 mg/kg. The bodyweight gain was also reduced regarding controls during the whole gestation at 15 mg/kg and at initial gestation at 10 mg/kg. The caesarean data for F1 litters revealed a significant decrease in the number of implantations in those dams dosed with 15 mg/kg, reducing the litter size. Pup viability (0-4 days) and the average pup bodyweight were also statistically reduced at 15 mg/kg. Litter retrieval decreased statistically in this group of dosing.

For F1 pups, eye opening, auditory response and preputial separation were not modified after amfenac treatment. Others, such as surface righting response, cliff aversion, startle response, vaginal opening and open field testing varied compared to controls at the dose of 10 mg/kg/day, but not at 15 mg/kg. Pinna detachment retarded in a dose-related manner at 15 and 30 mg/kg. T-maze testing data revealed increase in the time of memory recall in males at 15 mg/kg. In learning trials, an increased time occurred in trial day 1 and 4 in females at 3 and 10 mg/kg and at trial day 4 in females at 15 mg/kg.

F1 males showed reduced bodyweight at 10 and 15 mg/kg and were different from controls until day 114 and 126, respectively. However, the females showed statistical reduction of the bodyweight only after 15 mg/kg administration and until day 38 of exposure. However, no clinical signs were adverted.

In addition, evaluation of the precoital interval, fertility index, gestation length and the number of implantations did not show abnormalities. At scheduled necropsy, there were no noticeable gross lesions.

Litter data (F2) did not show any adverse effect regarding litter size, sex ratio, no. litters with live offspring and viability index. F2 weight was not affected in this generation. In addition, no clinical signs were developed. At scheduled necropsy no gross abnormalities were observed.

A parental NOAEL was not selected based on the evidence of toxicity at all dose levels. The NOAEL for the offspring could be established in 3 mg/kg bw/day.

- **Local tolerance**

Local tolerance was tested in a 1-month study in rabbits with experimental corneal incisions and in the course of the 3-month repeat-dose toxicity study in monkeys. Whereas the vehicle used for the rabbit study contained glycerine in place of mannitol, the final formulation was employed in the monkey study. In both studies, the suspension was well tolerated at dose levels up to 1.6 mg/day (4 x 40 µL x 10 mg/mL), which is 7-fold higher than the maximum human exposure.

Based on in the guinea pig maximization test Amfenac amide demonstrated no significant potential to cause hypersensitization.

- **Other toxicity studies**

Immunotoxicity

No special immunotoxicity studies were conducted with amfenac amide. The weight of evidence suggested that the standard toxicity studies can be considered enough to assess the immunotoxic potential of amfenac amide and no additional immunotoxicity studies were considered to be required.

Dependence

Amfenac amide, as an NSAID, is not considered a CNS-active medicinal product and therefore no dependence studies are considered to be necessary.

Impurities

Nepafenac has two impurities that have specifications beyond ICH biological qualification limits. Impurity AL-12384 present in the drug substance was biologically qualified in the rabbit topical ocular, rat systemic dosing, and reproductive studies conducted with nepafenac. Impurity AL-39187A present in the drug product did not elicit any signs of ocular or systemic toxicity in the one-month topical ocular rabbit study. With regard to complete genotoxicity package the weight of evidence suggests that the risk of mutagenic potential for AL-39187A can be considered low.

Photosafety

Nepafenac absorbs light in the visible spectrum and is topically applied to the eye. According to the CHMP Note for Guidance on Photosafety it should therefore be tested for phototoxicity, photoallergy, photogenotoxicity and photocarcinogenicity. The only study submitted is a conventional 3T3 BRU PT phototoxicity test, which was unequivocally negative. Photocarcinogenicity testing is not warranted given the short duration of treatment. With regard to photogenotoxicity, according to EMEA/CPMP/SWP/398/01, Note for Guidance on Photosafety Testing, the recognised photochemical genotoxicity reactions are strongly clastogenic in nature and suggest that a test for photochemical clastogenicity be conducted, e.g. an *in-vitro* chromosome aberration assay. Nepafenac demonstrates a positive response in this *in-vitro* model in the absence and presence of metabolic activation following 44 hours of exposure. Since it is likely that the assay will have a positive response for the test conditions conducted both in the absence and presence of a UV light source, the results would not provide valid information regarding the *in-vitro* photogenotoxic potential of nepafenac. A warning to avoid sunlight during treatment with NEVANAC has been included in the SPC and the PL.

Ecotoxicity/environmental risk assessment

The environmental risk assessment was carried out in accordance with the current guideline. Since the logK_{ow} for nepafenac is <4.5 (2.1), screening for persistence, bioaccumulation and toxicity is not

required. Based on the maximum human exposure of 0.24 mg/day and a default penetration factor of 0.01, $PEC_{\text{surface water}}$ is estimated at 0.0012 µg/L of nepafenac, which is one order of magnitude below the stipulated action threshold of 0.01 µg/L. Given the limited exposure, NEVANAC is unlikely to pose a risk to the environment.

4. Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

Pharmacokinetics

Alcon conducted 4 clinical pharmacology studies (C-04-08, C-05-08, C-05-19, C-04-27) to characterize the pharmacokinetics and disposition of nepafenac:

- Study C-04-27 was a single-centre, single-dose pharmacokinetic study to evaluate excretion and recovery of drug-related radioactivity and metabolic profiles of ^{14}C -nepafenac. The results of this study show that drug-related radioactivity is eliminated primarily by renal mechanism after oral administration of ^{14}C -nepafenac. The mean total recovery of radioactivity from the urine and feces was about 91.7%. Metabolic profiles of plasma and urine samples demonstrated that nepafenac is extensively metabolized and that metabolites circulate as glucuronide conjugates, except amfenac. These findings suggest that metabolism is the main route of nepafenac elimination.
- Study C-04-08 was a single-centre, multiple-dose, double-masked, randomized, parallel group study aimed to characterise the single- and multiple-dose (steady-state) pharmacokinetics of nepafenac 1 mg/ml and amfenac 16 healthy subjects following topical ocular administration. Nepafenac 1 mg/ml was administered to both eyes TID for 3 days with a final morning dose on Day 4. Quantifiable concentrations of nepafenac and amfenac were observed at the first sampling time (10-min) following single dose administration in the majority of subjects. Nepafenac and amfenac reached plasma C_{max} , on average, within 0.21 ± 0.08 hours and 0.48 ± 0.10 hours post-dose, respectively. The mean plasma C_{max} values were 0.276 ± 0.146 ng/ml and 0.293 ± 0.107 ng/ml for nepafenac and amfenac, respectively. The mean plasma concentrations declined with a mean $t_{1/2}$ of 1.1 ± 0.4 hours for nepafenac and 1.5 ± 0.5 hours for amfenac.

Following multiple dose administration, measurable concentrations of nepafenac (≥ 0.025 ng/ml) and amfenac (≥ 0.05 ng/ml) were observed at the first sampling time (10 min) in the majority of subjects. Nepafenac and amfenac reached plasma C_{max} , on average, at 0.25 ± 0.10 hours and 0.55 ± 0.14 hours post-dose, respectively. The mean plasma C_{max} values were 0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml for nepafenac and amfenac, respectively. After the peak, plasma concentrations of nepafenac and amfenac declined with a mean $t_{1/2}$ of 0.9 ± 0.2 hours and 1.6 ± 0.3 hours, respectively.

Based on the steady-state/single-dose ratio of individual C_{max} values, the accumulation index was approximately 1.34 for nepafenac and 1.61 for amfenac; overall, there were no unexpected changes in the pharmacokinetics of nepafenac or amfenac after multiple topical ocular administration of nepafenac 1 mg/ml. Based on the observed trough values, the steady-state pharmacokinetics is achieved by Day 2 following TID dosing.

From the data provided, the expected systemic exposure to nepafenac and its active metabolite (amfenac) following topical ocular administration of nepafenac 1mg/ml TID is low, and far from that observed when amfenac is used for the treatment of systemic inflammation/pain at the recommended dose (i.e. 50mg).

- Study C-05-08 was a single-centre, multiple-dose, double-masked, randomized, parallel group study in healthy adults Japanese subjects to characterize the single- and multiple-dose (steady-state) pharmacokinetics of nepafenac and amfenac. Eligible subjects were randomized to nepafenac 1 mg/ml (8), nepafenac 3 mg/ml (7), or Vehicle (4). Subjects received one drop of test article in each eye TID for 14 days with the last dose in the morning of Day 15. The results of this study are consistent with those seen in Caucasian healthy subjects and demonstrate that systemic exposure to nepafenac/amfenac following topical ocular administration of nepafenac 1mg/ml TID is low and far from that observed in patients who receive 50mg oral doses of amfenac. These findings indicate that there are no clinically meaningful ethnic differences in the systemic exposure of either nepafenac or amfenac following topical ocular administration of nepafenac 1 mg/ml. Consistently, accumulation if any might be minor. These findings also suggest that nepafenac C_{max} and AUC_{0-inf} values are dose proportional.

Therefore, taking into account that the margin of safety will even be greater in clinical practice, since patients receiving nepafenac 1 mg/ml will typically dose one eye, not both as done in this study, systemic exposure might be even lower, which is reassuring.

- Study C-05-19 was a multi-centre, open-label, single-dose, randomized, parallel-group design in adult patients who required cataract surgery. The objective of the study was to measure aqueous humor concentrations of nepafenac and amfenac or ketorolac following 1 drop of nepafenac 1 mg/ml or ketorolac 4 mg/ml, respectively, before cataract surgery.

After a single ocular drop of nepafenac 1 mg/ml, the maximum mean concentrations of nepafenac (177ng/ml) and amfenac (44.8 ng/ml) were observed at 1 hour post-dose. The peak mean concentration of ketorolac (37.4 ng/ml) was observed at 45 minutes post-dose. These data suggest that the timing of the sampling were insufficiently extended to properly assess the PK profile of nepafenac/amfenac in aqueous humor so that higher concentrations of nepafenac and amfenac might have been achieved. In order to further characterise the intraocular PK profile of nepafenac following topical ocular administration, a new PK and PD single-dose study has been conducted (Study C-05-19). Aqueous sampling was collected up to 4 hours post-dose. These data show that nepafenac is rapidly absorbed, reaching C_{max} in 30 min, while the C_{max} of its active metabolite, amfenac, is reached at 180 min following topical ocular administration of nepafenac. Total exposure to amfenac was similar to that of ketorolac 4mg/ml. Despite the observed differences between ketorolac and amfenac in the time needed to achieve the peak plasma concentrations, considering the proposed posology (starting before surgery), it is quite unlikely that these differences would be of clinical relevance (i.e. in the start of the analgesic/anti-inflammatory activity of both compounds).

The concentration to COX-1 and COX-2 IC₅₀ ratios for amfenac (0.649 and 1.07) were approximately 200% and 900% higher, respectively, than those for ketorolac (0.302 and 0.116). The ratio for nepafenac to COX-1 IC₅₀ was much lower (>50-fold) than that for amfenac.

The observed results suggest that a lower dose of nepafenac probably might have achieved sufficient efficacy with a better safety profile.

- Dose proportionality and time dependencies

- Special populations

Considering the intended route of administration and that systemic exposure is limited, specific studies in patients with renal or hepatic impairment were not deemed necessary.

Gender was not studied as a primary objective. Two pharmacokinetic studies (C-04-08, C-05-08) enrolled both male and female subjects. This allowed additional data analyses to examine potential gender effects on the pharmacokinetics of nepafenac and amfenac. Results show that apparent gender differences observed in the plasma pharmacokinetics of nepafenac and amfenac were small and not clinically relevant.

Pharmacokinetics in the elderly has not been specifically studied. Considering that this treatment is intended for the prevention and treatment of inflammation and pain secondary to cataract surgery, elderly patients are expected to be the main target population. This population has been extensively represented in the main studies presented to support the current Marketing Authorisation Application (MAA) and although a comparative analysis of the efficacy/safety profile as compared to younger patients have not been performed, data provided allow concluding on the benefit/risk of this product in the target population and thus, additional PK data are not deemed necessary.

Paediatrics has not been included in the studies supporting the MAA for NEVANAC. The Applicant argues that specific studies in this population are not needed necessary because cataract surgery is not common in children. In those situations where anterior surgery is conducted on children, since they are more sensitive to post-operative inflammation, the use of steroids is the current standard of care for paediatrics patients and it might be considered unethical to withhold steroids from this population.

- Pharmacokinetic interaction studies

Taking into account the expected systemic exposure to nepafenac/anfenac following topical ocular administration, systemic interactions would be unlikely. Data from *in vitro* studies adds reassurance to this conclusion.

- Pharmacokinetics using human biomaterials

In freshly dissected rabbit tissue preparations, the hydrolase activity of the retinal-choroidal tissue was 9- and 22-fold greater than that of the iris-ciliary body and the corneal tissue, respectively. Similar to human ocular tissues, amfenac production in rabbit ocular tissues increases linearly in a concentration- and time-dependent manner.

The activity of hydrolase in human ocular tissues was lower than hydrolase activity in freshly dissected ocular tissues from the rabbit. The difference is likely a post-mortem artefact, as these enzymes decay rapidly following death. In addition, enzyme decay appears to be particularly prevalent in ocular neuronal tissues upon enucleation and storage.

Overall, these data show that nepafenac exhibits enhanced corneal tissue permeability, and that the prodrug undergoes relatively rapid bioactivation to amfenac by intraocular hydrolases.

Pharmacodynamics

No specific pharmacodynamic studies in human have been performed. Available data come from pre-clinical studies and are discussed in the corresponding section.

- Mechanism of action

Nepafenac is an amide prodrug form of the nonsteroidal anti-inflammatory drug, amfenac. Nepafenac exhibits rapid corneal penetration and readily undergoes intraocular bioactivation by intraocular hydrolases to the pharmacologically active amfenac. While nepafenac is intrinsically a weak inhibitor of cyclooxygenase, amfenac potently inhibits cyclooxygenase. Following once-daily topical administration, sustained suppression of prostaglandin synthesis is observed for a period of more than 6 hours in the iris/ciliary body. Similar inhibitory effects are observed *ex vivo* in tissue of the retina/choroid.

Clinical efficacy

The clinical development plan to demonstrate the efficacy of nepafenac 1 mg/ml Eye Drops, Suspension for the proposed indication of prevention and treatment of pain and inflammation

associated with cataract surgery consisted of 6 clinical trials (C-95-93, C-97-30, C-02-53, C-03-32, C-04-65 and C-04-41).

Table 3 Summary of Completed Clinical Studies Supporting the Efficacy of nepafenac 1 mg/ml Eye Drops, Suspension

Study # Study Type / Location	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. of Sites	No. Patients Randomized
C-95-93 Dose-Response USA	Randomized, double-masked, Placebo-controlled	14 days	Patients, 18 years of age and older, having had cataract extraction with implantation of a posterior chamber IOL, and presenting with inflammation on Day 1 post-surgery	Nepafenac 0.3 mg/ml Nepafenac 1 mg/ml Nepafenac 3 mg/ml Placebo	1 drop QID	15	280
C-97-30 Dose-Response USA	Randomized, double-masked, Placebo-controlled	14 days	Patients, 18 years of age and older, having had cataract extraction with implantation of a posterior chamber IOL, and presenting with inflammation on Day 1 post-surgery	Nepafenac 0.03 mg/ml Nepafenac 0.1 mg/ml Nepafenac 0.3 mg/ml Nepafenac 1 mg/ml Placebo	1 drop QID	9	197
C-02-53 Posology / Safety and Efficacy USA	Randomized, double masked, Placebo-controlled	16 days	Patients, 18 years of age and older, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens	Nepafenac 1 mg/ml Placebo	1 drop: QD BID TID	10	220 ^a
C-03-32 Safety and Efficacy USA	Randomized, double masked, Placebo-controlled	16 days	Patients, 18 years of age and older, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens	Nepafenac 1 mg/ml Placebo	1 drop TID	21	487 ^a
C-04-65 Safety and Efficacy Europe (FR, HU, IT, PT, SP, UK)	Randomized, double-masked, active- and Placebo-controlled	23 days	Patients, 18 years of age and older, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens	Nepafenac 1 mg/ml Ketorolac 5 mg/ml Placebo	1 drop TID 1 drop TID 1 drop TID	15	227
C-04-41 Safety and Efficacy USA	Randomized, double-masked, active-controlled	Up to 30 days	Patients, 10 years of age and older, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens	Nepafenac 1 mg/ml Ketorolac 4 mg/ml	1 drop TID 1 drop QID	10	267 ^a

^a An additional 8 patients in C-02-53, 35 patients in C-03-32 and 16 patients in C-04-41 were consented and randomized but did not use study medication

- Dose response studies

Two dose response, randomised, double-masked, placebo-controlled studies have been performed to assess the efficacy of different concentrations of nepafenac, Eye Drops (0.3mg/ml, 1mg/ml, 3mg/ml, in Study 95-93 and 0.03mg/ml, 0.1mg/ml, 0.3mg/ml and 1mg/ml in Study 97-30) relative to placebo (vehicle) in adult patients having had cataract extraction with IOL replacement who presented with inflammation the day after (defined as flare score ≥ 2 or cells + flare score ≥ 4). Patients were dosed 4-times daily for the first 2 weeks and were assessed on D4, 8 and 15. The studied population appears representative of the target population, with the vast majority of patients being above 65 years old. Efficacy was assessed by means of changes from baseline in inflammatory parameters such as aqueous cells and flares scores. As a more intuitive measure of the clinical relevance of the observed effect, a responder analysis using the rate of cure (summed score of aqueous cells and flare equal to zero) and the rate of failure (summed score equal or greater than the baseline's score) have also been provided.

Overall, study design is considered appropriate to assess the effect on inflammation at different dose levels. The issued endpoints are all state-of-the-art. Notably, the rationale to select the proposed range of doses is lacking.

A total of 280 subjects were evaluable for the ITT analyses (N = 70, 70, 68, and 72 for the 0.3 mg/ml, 1 mg/ml, 3 mg/ml, and Placebo groups, respectively) in Study C-95-93. Even though these studies does not show impressive results, superiority of nepafenac over placebo in the treatment of inflammation following cataract surgery based upon clinical assessments of aqueous cells and flare was demonstrated. The cure rate, around 30 %, was also significantly higher than for vehicle, which was just below 20 %.

The data provided do not show the presence of a dose-response relationship. In fact, no apparent differences among treatment groups were seen for the inflammatory assessment. Considering the analysis of responders (percentage of cure), the lower doses tested, i.e. nepafenac 0.3mg/ml and 1mg/ml QID, showed better results than the higher one and thus, considered suitable doses to be further studied.

Similar conclusions can be drawn from Study C-97-30, in which two additional lower doses were tested (nepafenac 0.03mg/ml and 0.1mg/ml in addition to nepafenac 0.3mg/ml and 1mg/ml QID). All the doses tested showed statistically significant superiority of nepafenac over placebo for the inflammatory endpoints (aqueous cells, flare and aqueous cells+flare), with no differences between doses. The cure rate varied between 15% and 32 % in the active groups versus 7.7 % in the vehicle group at Day 15 (p=0.042). An assessment of the clinical relevance of the observed effect by means of the rate of cure and failures, shows minor differences between doses so that the intermediate doses tested of nepafenac (i.e. 0.3mg/ml and 1mg/ml) could be considered optimal from an efficacy point of view, to be further tested in the confirmatory trials.

However, only the 1mg/ml dose of nepafenac has been selected for the confirmatory trials. The Applicant claims that this decision was based not only on efficacy/safety grounds but also on quality issues, i.e. this was the lowest concentration which exhibited acceptable long-term product stability. Although theoretically a lower dose (i.e. 0.3mg/ml) might be more suitable, since there were no safety concerns, the proposed dose can be considered acceptable.

- Main studies

Title of Study

C-02-53

Topical preoperative and postoperative use of nepafenac ophthalmic suspension 0.1 % for treatment of anterior segment inflammation after cataract/IOL surgery

C-03-32

Preoperative and postoperative use of nepafenac ophthalmic suspension 0.1 % for the treatment of ocular inflammation associated with cataract surgery.

C-04-65

Nepafenac 0.1 % eye drops suspension compared to ketorolac Trometamol 0.5 % eye drops solution, and placebo (nepafenac vehicle) for the prevention and treatment of ocular inflammation and ocular pain associated with cataract surgery: European study.

C-04-41

Preoperative and postoperative NEVANAC (nepafenac ophthalmic suspension) 0.1 % compared to Acular LS TM for the treatment of ocular inflammation associated with cataract surgery.

METHODS

Study Participants

Individuals over the age of 18 (over age 10 for C-04-41) who had a cataract, and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens were included.

Patients with any intraocular inflammation (cells or flare greater than Grade 0) or ocular pain greater than Grade 1 in the study eye (operative eye) that was present during the screening slit-lamp examination were included. Those with chronic or recurrent inflammatory eye disease in the operative eye, patients, who in the opinion of the investigator, might have been at increased risk of complications from topical NSAIDs were excluded.

The use of concomitant topical and systemic anti-inflammatory agents was contraindicated. A washout period of a minimum of 14 days was required for steroids. For NSAIDs, the washout period was a minimum of 7 days. Patients who were taking a prophylactic daily dose of aspirin (up to 100 mg/day) prior to enrolling in the study were permitted to continue this therapy during the study. Patients were also permitted to take paracetamol.

Treatments

C-02-53

One drop of nepafenac ophthalmic suspension 0.1 % 1, 2 or 3 times daily beginning 1 day prior to cataract surgery and continuing for 14 days postoperatively. Furthermore, one drop was administered 30 – 120 minutes prior to surgery.

C-03-32

Nepafenac ocular suspension 0.1 % or vehicle was administered 3 times daily beginning 1 day prior to surgery and continuing for 14 days after the operation.

Prior investigation had shown a TID regimen numerically most effective.

C-04-65

The treatment was either nepafenac 1 mg/ml eye drops (suspension), Ketorolac Trometamol 5 mg/ml eye drops (solution), or nepafenac vehicle eye drops.

All groups commenced treatment one day before cataract surgery, with an additional drop on the day of surgery 30 to 120 minutes prior to the extraction procedure, and continued therapy for up to 21 days. The dosage was 1 drop 3 times daily. The afternoon dosage was to be applied within 1- 4 hours before the clinical evaluation on the of post- surgery examination days.

The medication was applied one day prior to the surgical procedure and was continued up to 21 days afterwards, i. e. the treatment was 23 days.

C-04-41

Application of study medication began at the day prior to cataract surgery. Nepafenac 0.1 % dosed was TID, and ketorolac, 0.4 % QID, in consistency with the approved regimen in the USA. In addition, 30-120 minutes before surgery an extra dose was administered, and at day 7 an additional drop of study drug was applied immediately before completing the patient's drop comfort evaluation. The duration of the treatment was planned to be at least 15 days and maximally 32 days.

Nearly all patients participating in the pivotal studies received antibiotic prophylaxis (to prevent endophthalmitis) according to clinical practice in each study centre, with no differences among treatment groups in the type of antibiotic used.

Objectives

C-02-53

To demonstrate that topical ocular nepafenac ophthalmic suspension 0.1 % given from 1 day before surgery, continuing on the day of surgery and for 14 days thereafter, is safe and effective in treatment of inflammation that occurs after cataract surgery with IOL implantation.

C-03-32

To demonstrate that topical ocular nepafenac ophthalmic suspension 0.1 % given 1 day before surgery, continuing on the day of surgery, and for 14 days after surgery decreases the incidence and severity of inflammation that occurs after cataract surgery and IOL implantation.

C-04-65

To evaluate the safety and efficacy of nepafenac 1 mg/ml eye drops suspension compared to placebo and Ketorolac Trometamol 5 mg/ml eye drops solution for the prevention and treatment of ocular inflammation and ocular pain after cataract extraction by phaco-emulsification with posterior chamber IOL implantation.

C-04-41

To evaluate the safety and efficacy of NEVANAC (nepafenac ophthalmic suspension) 0.1 % compared to Acular LS ophthalmic solution for the treatment of ocular pain and inflammation associated with cataract surgery.

Outcomes/endpoints

An overview of the primary and secondary endpoints used in the single trials is presented below.

Table 4

Efficacy Variables in the Nepafenac Eye Drops, Suspension Clinical Studies						
	C-95-93	C-97-30	C-02-53	C-03-32	C-04-65	C-04-41
Primary Efficacy Variable(s)	<ul style="list-style-type: none"> Cells score Flare score Inflammation score (cells + flare) 	<ul style="list-style-type: none"> Cells score Flare score Inflammation score (cells + flare) 	<ul style="list-style-type: none"> % Treatment failures^a 	<ul style="list-style-type: none"> % Cures at Day 14 	<ul style="list-style-type: none"> % Cures at Day 14 (Nepafenac vs. Placebo) 	<ul style="list-style-type: none"> % Clinical success at Day 14
Secondary Efficacy Variable(s)	<ul style="list-style-type: none"> % Cures % Treatment failures^a 	<ul style="list-style-type: none"> % Cure % Treatment failures^a 	<ul style="list-style-type: none"> Clinically significant inflammation % responders^a Cells score Flare score Cells + flare score 	<ul style="list-style-type: none"> % Clinically significant inflammation % with no pain % Treatment failures^b 	<ul style="list-style-type: none"> Cells plus flare Score at Day 21 (Nepafenac vs. Ketorolac 5 mg/ml) % Treatment failures^{b,4} Investigator assessment of ocular pain by visit^c % Patients with clinically significant inflammation^d Comfort at Day 7^e 	<ul style="list-style-type: none"> % Clinical cure % Clinical success by visit % Treatment failures^b % Clinically significant inflammation at each visit Cells score by visit Flare score by visit Cells plus flare score by visit Ocular pain at each visit (patient and investigator) Photophobia at each visit Corneal staining at each visit Comfort (day before surgery and at Day 7) Overall patient satisfaction with study medication

Sample size

C-02-53

A number of 48 patients per group would ensure 80 % power to detect a difference in the percent of patients who were treatment failures, if the percent in the active and placebo group was 32.6 % and 63 %, respectively.

C-03-32

A number of 218 patients per treatment group would allow a power of 90 % to detect a difference of percent cured patients if the cure rate in the nepafenac group was 38.99 % and 24.14 % in the vehicle group.

C-04-65

In an earlier trial the percentage of patients cured at Day 14, was 62.6 % and 17.2 %, respectively, with a sample size of 243 and 233 patients. The lower 95 % confidence limit for nepafenac was 56.52 % and the upper confidence limit was 22.05 % for placebo. Using these criteria, a sample size of 46 evaluable patients per group yielded 90 % probability to detect a significant treatment difference between the active and placebo treatment. In the same study > 2 unit mean difference in cells + flare between nepafenac and placebo was observed (at Day 14). The standard deviation was 1.4 units with an upper 95 % confidence limit of 1.54 units. Using the 1.54 unit standard deviation 62 evaluable patients per arm would correspond to non-inferiority of nepafenac to ketorolac. The non-inferiority criterion of 1.0 unit was chosen as this was the smallest measurable increment. The probability coverage was 90 %.

C-04-41

A number of 130 evaluable patients per treatment arm would ensure a greater than 80 % probability that the 95 % lower confidence limit for the difference in proportions would be greater than – 20 at Day 14. This assumed 60 % of patients with clinical success for both nepafenac and ketorolac.

Randomisation

C-02-53

Patients were randomly assigned to the treatment groups nepafenac TID, BID, QD, and vehicle in a 1:1:1:1 distribution.

C-03-32

Treatment was stated to be allocated 1:1 in the two groups.

C-04-65

A 1:1:1 ratio was used in the randomisation.

C-04-41

A 1:1 randomisation was used.

Blinding (masking)

Studies C-03-32, C-04-65 and C-04-41 were all double masked and the study medication was supplied in identical containers in all studies.

True double-dummy masking was not used in Study C-02-53 in order to minimise the possibility of patients dosing from the incorrect bottle. Efforts to minimise bias were made, i.e. the efficacy/safety assessment was done by an investigator not involved in the study drug dispensation and patients were blinded to treatment active/placebo (but not to treatment regimen), although the existence of bias can not be completely ruled out.

In study C-04-65, the comparator drug was the one approved in the participating countries. The marketed ketorolac eye drops were sterile transferred to a DROP-TAINERS®.

Statistical methods

C-02-53

Fischer's exact test (3-tests with TID, BID and QD versus placebo) was used in this superiority trial. The effect of multiplicity testing was investigated with Hommel's procedure. Also, the secondary endpoints were tested with 3-tests.

C-03-32

The trial was a superiority study and the two groups were to be compared with Fischer's exact test. The incidence of treatment failures, clinically significant inflammation and no pain and were compared with logistic regression.

C-04-65

The superiority analyses used ITT population whereas the non-inferiority analyses were based on the PP-population.

C-04-41

This trial was a non-inferiority study. A 2-sided 95 % confidence interval was constructed for the difference in proportions between the two treatment groups and non-inferiority was declared if the lower confidence limit for the treatment group difference (nepafenac – ketorolac) was greater than – 20 %. The PP data set was to form the basis of conclusion.

RESULTS

Participant flow

C-02-53

Of the 228 patients randomized in this study, 96 discontinued from the study for the following reasons: adverse event (6), patient decision (9), lost to follow-up (1), treatment failure (70) and other (10). The Applicant claims that the high number of treatment failure discontinuations was anticipated in the Vehicle group because for the patient's safety, investigators were required to exit patients from the study if inflammation reached a preset level in order to initiate rescue medication, since this was a placebo-controlled study. However, a high proportion of patients also discontinued in the nepafenac treatment groups due to treatment failure.

C-03-32

A total of 487 patients received test article and were therefore were evaluable for the safety analysis. A total of 476 patients were evaluable for the intent-to-treat analysis (243 nepafenac and 233 Placebo). Of the patients evaluable for the intent-to-treat analysis, 33 were not evaluable for the per protocol analysis due to a significant protocol violation (n=27) or a complicated/difficult surgery (n=6). Therefore, a total of 443 patients were evaluable for per protocol analysis.

Of the 522 patients randomized in this study, 218 discontinued from the study for the following reasons: adverse event (7), patient decision (23), non-compliance (2), treatment failure (158), and other (28).

C-04-65

Two hundred twenty-seven patients were randomized to treatment at 15 study sites. All 227 patients enrolled into the study received study medication and were included in the safety analysis. Of the 227 patients who received study drug, 2 patients were excluded from the intent-to-treat analyses, as they had no on-therapy postoperative study visits. This resulted in a total of 225 patients evaluable for the intent-to-treat analysis of efficacy (76 nepafenac, 73 ketorolac, 76 Placebo). Of the 225 patients evaluable for intent-to-treat analysis, 2 patients were excluded from all per protocol analyses due to prohibited concomitant medication usage that had the potential to affect efficacy results. Therefore, 223 patients were evaluable for the per protocol analysis of efficacy (76 nepafenac, 72 ketorolac, 75 Placebo).

Of the 227 patients randomized in this study, 23 discontinued from the study for the following reasons: adverse event (7), decision unrelated to an adverse event (1), treatment failure (14) and surgical complications requiring additional anti-inflammatory therapy (1).

C-04-41

Two hundred eighty-three patients were randomized to treatment at 10 study sites in the US. Sixteen patients who did not receive study medication and discontinued from the study prior to surgery were excluded from all analyses. Thus, 267 patients were evaluable for the safety analyses. Of the 267 patients who received study drug, 3 patients were excluded from the intent-to-treat analyses, resulting in a total of 264 patients evaluable for the intent-to-treat analysis of efficacy (131 nepafenac and 133 ketorolac 4 mg/ml).

Of the 264 patients evaluable for intent-to-treat analysis, 8 patients were excluded from all per protocol analyses due to improper study medication usage that had the potential to affect efficacy

results. Therefore, 256 patients were evaluable for the per protocol analysis of efficacy (127 nepafenac and 129 ketorolac 4 mg/ml).

Of the 283 patients randomized in this study, 59 discontinued from the study for the following reasons: adverse event (4), patient decision (13), non-compliance (4), treatment failure (6) recurrent inflammation requiring anti-inflammatory therapy in a previous clinical success patient (16) and other (16).

Recruitment

See Table 2.7.3.1-9

Conduct of the study

C-02-53

No major amendments were issued. An exploratory post-hoc evaluation of percent cures and pain was conducted.

C-03-32

No protocol amendments were issued. Exploratory post-hoc analysis of ocular was conducted.

C-04-65

No changes to the protocol or planned statistical analyses were employed.

C-04-41

A few minor protocol amendments were issued.

Baseline data

C-02-53

The mean age was 70.3 years (47-91). Other baseline characteristics are shown in the table above.

C-03-32

The mean age was 69.9 years (27-90).

C-04-65

The mean age was 72.1 years (42-90). Other demographic variables are shown in the table above. Baseline characteristics were well distributed among the three treatment groups.

C-04-41

The mean age was 69.4 years (43-89). Other demographic information is located in the table above.

Numbers analysed

C-02-53

A number of 228 patients were randomised of whom 8 discontinued prior to surgery, and, thus, were excluded from all analyses. Of the 220 patient 8 patients discontinued prior to or during surgery (all judged unrelated to study medication), thus, 212 patients were available for the ITT analysis. A number of 14 were excluded to analysis because of protocol deviations or non-compliance with study medication. The PP-population encompassed 198 patients.

C-03-32

A total of 487 patients were recruited, of whom 11 were excluded because of lack of on-therapy visits. (withdrawal of consent prior to surgery, use of prohibited medication, non-compliance with study medication, surgical complication requiring steroid therapy, and lost to follow up). This left 476 for the ITT population. A number of 33 patients were excluded from PP analysis because of significant protocol violation or complicated surgery. This left 443 to the PP population.

C-04-65

A number of 227 patients were randomised of whom 225 participated in the ITT population, as 2 patients did not have any post-operative on-treatment visits. Two patients used “prohibited” medication, thus the PP population encompassed 223 patients.

C-04-41

A number of 283 patients were randomised to treatment, of whom 16 did not receive study medication. Out of those 267 patients, 3 did not have on-therapy postoperative study visits as 2 were discontinued prior to surgery and 1 had a protocol variation, thus, 264 patients were included in the ITT population. A number of 8 patients were excluded because of incorrect use of study medication. Thus, 256 patients were available for the PP population.

Outcomes and estimation

C-02-53

The primary efficacy variable was the percent of patients declared treatment failures at the Day 14 Visit. Treatment failure was defined as an aqueous cells score ≥ 3 , an aqueous flare score ≥ 3 , or an ocular pain score ≥ 4 . Aqueous cells were graded on a 5-point scale, aqueous flare on a 4-point scale, and ocular pain on a 6-point scale.

Table 5

**Table 11.4.1.1.-1:
Cumulative Percent of Treatment Failures at Day 14 by Treatment
(Intent-to-Treat)**

	Total Patients	Treatment Failures		Fishers P-Value	Raw P-Value	Hommel P-value
		N	%			
Nepafenac 0.1% QD	48	12	25.0	<0.0001*	0.0004*	0.0007*
Nepafenac 0.1% BID	50	15	30.0		0.0020*	0.0020*
Nepafenac 0.1% TID	56	11	19.6		<0.0001*	<0.0001*
Vehicle	58	35	60.3			

Overall P-value is from Fishers Exact test.

Raw P-values reflects treatment comparisons to Vehicle.

Hommel P-value reflects treatment comparisons to Vehicle controlling for the overall familywise error rate.

While all evaluated dosing regimens (QD, BID and TID) were associated with a statistically lower incidence of treatment failures than Placebo ($p < 0.0001$), the TID-dosed nepafenac group exhibited the fewest treatment failures. The lowest treatment failure rate was observed in the nepafenac TID group (19.6%), followed by the nepafenac QD (25.0%) and nepafenac BID groups (30.0%), respectively. The highest treatment failure rate was observed in the Vehicle group (60.3%). Consistent results were seen in the PP analysis (TID 16.7% compared to BID 26.1%, QD 27.3%, or Vehicle 61.1%). In Study C-02-53, the discontinuation rate due to treatment failures ranged from 20% to 28% for the nepafenac QD, BID and TID treatment groups.

The TID-dosing had the highest percentage of patients with no ocular pain and proportion of treatment responders at all visits as well as the lowest rates of clinically significant inflammation at all visits. Even though most of these differences cannot be considered clinically relevant, these results together with the lower rate of treatment failures support the selection of the three times daily as the optimal dosing of nepafenac 1 mg/ml Eye Drops, Suspension.

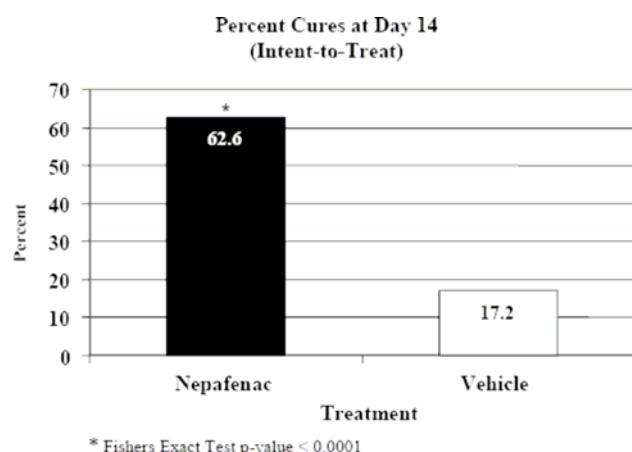
Secondary endpoints support the efficacy of nepafenac Ophthalmic Suspension, 0.1% as demonstrated by lower aqueous cells scores, lower aqueous flare scores, lower cells plus flare scores, a lower percent of patients with clinically significant inflammation (cells plus flare scores ≥ 4) and a greater percent of patients who were treatment responders (defined as aqueous cells < 1 and aqueous flare = 0). As observed in the primary efficacy analysis, statistically significant differences supporting a TID dosing regimen for nepafenac Ophthalmic Suspension, 0.1% were observed in these secondary efficacy analyses.

C-03-32

The primary efficacy variable was percent cures (defined as cells + flare score = zero) at Day 14.

The results showed that nepafenac 1 mg/ml Eye Drops, Suspension was superior to Placebo in the prevention and treatment of ocular pain and inflammation associated with cataract surgery based upon clinical assessments of aqueous cells, flare and ocular pain. Up to 62.6% of patients treated with nepafenac were cured (defined as no signs of inflammation) after two weeks of treatment as compared to 17.2% in the placebo arm. The rate of failures at D14 was 8.2% in nepafenac vs 61% in placebo. At day 1 postsurgery, 83% of patients in nepafenac were free of pain as compared to 41.6% of patients in placebo, increasing to 93% after two weeks of treatment with nepafenac.

Results of the primary efficacy variable are shown below.



C-04-65

The primary efficacy variable was the percent cures at Day 14, where cure was defined as aqueous cells score = 0 and flare score = 0 at Day 14 and all subsequent visits.

Nepafenac 1mg/ml tid was statistically significantly superior to placebo on the treatment of ocular inflammation, as measured by the rate of cure at D14 (76% vs 59% in nepafenac and placebo, respectively) and ocular pain (percentage of pain-free patients at D14 were 86% vs 63% in nepafenac and placebo, respectively). Notably, the rate of failures was quite low in both groups (3.9% vs 11.8% in nepafenac and placebo, respectively), especially in placebo, as compared to the previous study (61% vs 8.2%, respectively). Nepafenac showed consistent results to those seen in the previous study.

Although superiority of nepafenac over placebo could be demonstrated, the clinical relevance of the observed differences could be questionable, probably due to the higher placebo response observed in this study.

The non-inferiority of nepafenac relative to ketorolac trometamol, defined by a delta margin of 1 point in the mean cells+flare score at D21, was demonstrated. Even though, the delta margin is considered broad and despite previous concerns on the clinical relevance of the observed effect, the results of this study demonstrate that nepafenac 1mg/ml TID has a similar anti-inflammatory and pain relief efficacy compared to a currently authorised treatment for the claimed indication (i.e. ketorolac trometamol 5mg/ml TID, used according to the most commonly authorised regimen in the EU).

Results for the primary endpoint are shown in the table below.

Table 6

Percent Cures at Day 14 by Treatment for Nepafenac versus Placebo
(Intent-to-Treat)

Treatment	Total N	Day 14 Clinical Cures		P-Value ^a
		N	%	
Nepafenac	76	58	76.3	0.0241
Placebo	76	45	59.2	

^a Test = Chi-square (Fishers Exact test if N<5)

The corresponding figures for the PP population are 59 (77.6 %) and 43 (61.4 %), respectively (p=0.0330). Robustness of the results has been demonstrated.

Secondary efficacy evaluations also indicated that nepafenac 1 mg/ml Eye Drops, Suspension was non-inferior to ketorolac 5 mg/ml Eye Drops, Solution for: inflammation (mean cells and flare scores) at the postoperative Day 21 visit. The non-inferiority criterion of 1.0 unit was chosen because it is the smallest measurable increment on the cells + flare scale, implying that differences smaller than this are not measurable for an individual patient and therefore not clinically meaningful.

Furthermore, the results of all other evaluations indicated that nepafenac 1 mg/ml was clinically equivalent to ketorolac 5 mg/ml, with superiority shown over ketorolac 5 mg/ml for: clinical success rate at Day 14, percent pain-free patients at Day 3 and comfort upon instillation of the eye drop at Day 7.

C-04-41

The primary efficacy variable was the percentage of patients who were a “clinical success” at Day 14, where a “clinical success” was defined as aqueous cells score ≤ 1 (0 to 5 cells) and flare score = 0 at the current visit and all subsequent visits. Non inferiority was concluded if the lower 95% confidence limit for the difference in proportions of clinical success (nepafenac – ketorolac 0.4%) would be greater than -20% at Day 14.

This study was aimed at demonstrating the non-inferiority of nepafenac 1mg/ml tid as compared to ketorolac trometamol 4mg/ml QID by means of the anti-inflammatory effect (rates of clinical success defined as cells score ≤ 1 plus flare score=0 at D 14 and subsequent visits).

The non-inferiority of nepafenac relative to ketorolac trometamol, defined by a delta margin of 20% in the difference of clinical success rates between Nep-Ketor, was demonstrated. However, considering the observed rates of success at Day 14 (i.e. 64% nepafenac vs 65% ketorolac) the proposed delta margin is considered too broad to conclude on the non-inferiority. However, these results show similar anti-inflammatory effects of both treatments as measured by the rate of cures, the rates of clinical success and mean aqueous cells and flare scores as well as similar pain relief efficacy at all visits.

Although lower rates of cure were seen at D14 as compared to the previous study (nepafenac 43% vs ketorolac 36%), at D 28 similar rates were achieved. Therefore, this study confirms the previous conclusions on the non-inferiority of nepafenac relative to ketorolac.

Table 7

Percent Clinical Success at Day 14 by Treatment (Per Protocol)							
Treatment	Total ^b N	Day 14 Successes		Delta	Lower	Upper	P-Value ^a
		N	%				
Nepafenac	123	79	64.2	-0.5	-12.5	11.5	0.9314
Ketorolac 0.4%	122	79	64.8				

^a Test = Chi-square (Fishers Exact test if N<5)

^b 8 patients had missing percent clinical success data

The ITT results were similar to the presented PP results, confirming the robustness of the results.

The secondary efficacy evaluations of patient comfort and satisfaction also indicated that nepafenac was superior to ketorolac dosed 4 times a day for: drop comfort upon instillation one day prior to and 7 days following surgery, burning upon instillation, stinging upon instillation, soothing upon instillation and, redness upon instillation.

Ancillary analyses

- Analysis performed across trials (pooled analyses and meta-analysis)

An overall description of study populations and efficacy results across different studies has been performed, which summarised the available data but do not add relevant information.

- Clinical studies in special populations

As expected from the studied condition, elderly (>65 years old) patients have been extensively represented in the pivotal studies (86%) as well as the proportion of very elderly patients (around 50% of the elderly patients). No specific studies in children have been performed. In 1 study (C-04-41) patients as young as 10 years of age were eligible for participation; however, no paediatric patients participated in the study.

No clinically relevant or consistent differences in the effectiveness of nepafenac 1 mg/ml Eye Drops, Suspension have been observed based on age, sex, race or iris color.

No specific studies in hepatic or renal impaired patients have been performed. Considering that systemic exposure might be negligible, specific studies are not deemed necessary.

- Supportive studies

None

- Discussion on clinical efficacy

Four of the efficacy trials (C-95-93, C-97-30, C-02-53 and C-03-32) presented in this MAA were designed to follow patients for the first 2 weeks of the postoperative period. A reduction in aqueous cells and flare scores (C-95-93 and C-97-30), as well as an increase in the percent of patients cured (C-02-53 and C-03-32), was observed in the nepafenac treatment groups over the 14-day postoperative period.

One additional trial (C-04-65) was designed to treat patients for 23 days (1 day preoperatively, on the day of surgery and for 3 weeks postoperatively) with an off-treatment assessment 28 days postoperatively. A final trial (C-04-41) was designed to treat patients for up to 30 days (1 day preoperatively, on the day of surgery and for up to 4 weeks postoperatively) with an off-treatment assessment 28 days postoperative for all patients. Studies C-04-41 and C-04-65, which had off-therapy assessments for up to 2 weeks after treatment was stopped, demonstrated that patients generally remained free of inflammation once therapy was stopped.

Although the applicant acknowledges the lack of a clinical bridging study to support the choice of the 3 times daily dosing posology used in studies C-02-53, C-03-32, C-04-41 and C-04-65 compared to 4 times daily used in the initial dose-response studies C-95-93 and C-97-30, the totality of the evidence

suggests that little additional efficacy could be achieved with 4 times daily dosing. The proposed posology (TID) is supported by the results of Study C-02-53 and confirmed by the results of the pivotal studies, and the rationale provided to withdraw the 4 times daily regimen is considered acceptable by the CHMP.

According to the results of the pivotal studies, 14 days appears the optimal treatment duration since for the vast majority of patients a significant reduction in inflammatory parameters was achieved in two weeks of treatment. Although it is recognized that extending therapy for up to 21-28 days might provide some additional benefit from a purely inflammatory point of view in some patients, the clinical relevance of this added benefit is doubtful. Therefore, a 14 days treatment duration that could be extended for up to 3 weeks according to physician's judgement is considered a more consistent and justified recommendation. This is reflected adequately in the SPC Posology section (4.2).

Paracetamol use was variable prior to surgery across studies (ranging from 2.6% to 22.6%), with minor differences across treatment groups, whilst as expected the use of paracetamol was increased in the placebo groups following surgery. Overall, paracetamol use on the day of surgery or beyond ranged from 7.1% to 22% and was higher in the placebo arms with minor differences across active treatment groups. The reasons for taking paracetamol have not been provided and although ocular pain might be the main, the existence of other reasons is possible. From the data provided any conclusion on possible differences in pain relief between active treatments can not be drawn.

While the definition for treatment failure was identical in Studies C-02-53, C-03-32, C-04-41 and C-04-65, treatment failure served as the primary efficacy variable in Study C-02-53 and as a secondary efficacy variable in Studies C-03-32, C-04-41 and C-04-65. It is noted that the discontinuation rate because of treatment failure appears to be quite high in study C-02-53. Since treatment failure was the primary efficacy variable in Study C-02-53 in this initial Phase III study with nepafenac 1 mg/ml, it is possible that investigators may have been more attentive to the degree of inflammation and pain experienced by the patient.

The patients included in the study population are representative for the demographic population in the intended use of the drug.

In summary the efficacy of nepafenac eye drops 0.1 % suspension has been investigated in a well planned and well conducted clinical programme. An anti-inflammatory effect superior to that of placebo (nepafenac vehicle) and a non-inferior effect to the well established comparator ketorolac Trometamol (0.4 or 0.5 %, dosed 4 or 3 times daily, respectively) eye drops solution was demonstrated, applying to both established post surgery inflammation and preventing inflammation by the application of the study drug one day prior to cataract surgery. In conclusion, data provided support the efficacy of NEVANAC in the claimed indication.

Clinical safety

- **Patient exposure**

The evaluation of safety was conducted in 1,938 adult and elderly patients across 16 topical ocular clinical studies which included post-cataract inflammation studies (C-95-93, C-97-30, C-02-53, C-03-32, C-04-41, and C-04-65), comfort, safety, and pharmacokinetic studies (C-95-91, C-95-92, C-04-08, C-05-08, and C-05-19), macular edema studies (C-96-08, C-00-35, C-00-60, and C-00-61), and a post-excimer laser pain study (C-97-52).

Overall, 1678 patients enrolled in studies in the claimed indication. In the post-inflammation cataract studies, the proposed indication, 728 patients were exposed to nepafenac 1 mg/ml, hereof 515 (25% of the overall safety population) in the proposed TID posology.

The mean duration of exposure to nepafenac 1 mg/ml in the post-cataract studies was 19.9 days including the addition of a recently completed long-term safety study (C-05-20). One hundred sixty-six patients have now been exposed to nepafenac 1 mg/ml Eye Drops, Suspension for at least 21 days,

which included 47 patients exposed to nepafenac 1 mg/ml Eye Drops, Suspension for greater than 82 days. No safety issues were identified in those patients with a long-term exposure. Only few patients with macular oedema received nepafenac on a long-term basis.

The safety evaluation of nepafenac includes a comprehensive battery of examinations, both ocular and systemic, although not uniformly conducted in all patients as well as system.

Table 8

Frequency of Dosage Exposure to Study Drug - All Topical Ocular Clinical Studies
(C-95-91, C-95-92, C-95-93, C-96-08, C-97-30, C-97-52, C-00-35, C-00-60, C-00-61, C-02-53, C-03-32, C-04-08, C-04-41, C-04-65, C-05-08, and C-05-19)

Treatment	Total N	Four-Times-Daily (QID)		Three-Times-Daily (TID)		Twice-Daily (BID)		Once-Daily (QD)	
		N	%	N	%	N	%	N	%
Total	2010^a	703	35.0	1014	50.4	74	3.7	219	10.9
Nepafenac 3 mg/ml	141	78	55.3	39	27.7			24	17.0
Nepafenac 1 mg/ml	832	141	16.9	539	64.8	53	6.4	99	11.9
Nepafenac 0.3 mg/ml	127	127	100.0						
Nepafenac 0.1 mg/ml	41	41	100.0						
Nepafenac 0.03 mg/ml	40	40	100.0						
Ketorolac 5 mg/ml	73			73	100.0				
Ketorolac 4 mg/ml	163	134	82.2					29	17.8
Diclofenac 1 mg/ml	44	20	45.5					24	54.5
Nepafenac Vehicle	549	122	22.2	363	66.1	21	3.8	43	7.8

^aThe total number of patients evaluable for safety (N=1938) is less than the total shown because C-95-91 was a 4-period crossover study with a sample size of 24 patients in which each participant was exposed to a single administration dose of Nepafenac 3 mg/ml Eye Drops, Suspension, Nepafenac 1 mg/ml Eye Drops, Suspension, Diclofenac 1 mg/ml Eye Drops, Solution, and Nepafenac Vehicle Eye Drops

Table 9

Table 46-1:
Duration of Exposure to Study Drug - Post-Cataract Inflammation Studies
(C-95-93, C-97-30, C-02-53, C-03-32, C-04-41, C-04-65, C-05-20, and C-05-54)

Treatment	Total		1 to 3 Days		4 to 9 Days		10 to 16 Days		17 to 20 Days		21 Days		22 to 30 Days		31 to 82 Days		>82 Days	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	2041	150	7.3	200	9.8	940	46.1	327	16.0	23	1.1	250	12.2	23	1.1	128	6.3	
Nepafenac 3 mg/ml	68	0	0.0	4	5.9	63	92.6	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0	
Nepafenac 1 mg/ml	886	57	6.4	31	3.5	419	47.3	213	24.0	8	0.9	104	11.7	7	0.8	47	5.3	
Nepafenac 0.3 mg/ml	107	2	1.9	2	1.9	97	90.7	6	5.6	0	0.0	0	0.0	0	0.0	0	0.0	
Nepafenac 0.1 mg/ml	41	0	0.0	2	4.9	39	95.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Nepafenac 0.03 mg/ml	40	0	0.0	2	5.0	38	95.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Ketorolac 5 mg/ml	73	1	1.4	1	1.4	2	2.7	0	0.0	3	4.1	65	89.0	1	1.4	0	0.0	
Ketorolac 4 mg/ml	184	1	0.5	6	3.3	46	25.0	56	30.4	1	0.5	21	11.4	11	6.0	42	22.8	
Nepafenac Vehicle	642	89	13.9	152	23.7	236	36.8	51	7.9	11	1.7	60	9.3	4	0.6	39	6.1	

Patient C9730.1300.0111 (exposed to Nepafenac 0.1 mg/ml Eye Drops, Suspension) was lost to follow-up and had missing information pertaining to last instillation of study medication. The last visit date is used as the last date of exposure, and no medication was dispensed at the visit.

Patients C0332.1204.2502 and C0441.3807.1033 (exposed to Nepafenac 1 mg/ml Eye Drops, Suspension) did not dose with study medication the day before surgery.

Patients C0332.3899.1802, C0332.3899.1804, C0332.3899.1805, C0332.3899.1806, and C0332.3899.1809 (exposed to Nepafenac 1 mg/ml Eye Drops, Suspension) received 1 additional day of study medication prior to surgery.

Patient C0332.3889.1103 (exposed to Nepafenac 1 mg/ml Eye Drops, Suspension) received 2 additional days of study medication exposure prior to surgery.

Patients C0332.3899.1801, C0332.3899.1803, and C0332.3899.1807 (exposed to Nepafenac Vehicle Eye Drops) received 1 additional day of study medication prior to surgery.

Table 10

**Duration of Exposure to Study Drug - Macular Edema Studies
(C-96-08, C-00-35, C-00-60, and C-00-61)**

Treatment	Total	1 to 16 Days		17 to 30 Days		31 to 60 Days		61 to 90 Days		91 to 180 Days		>180 Days	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Total	53	0	0.0	1	1.9	6	11.3	27	50.9	7	13.2	12	22.6
Nepafenac 3 mg/ml	32	0	0.0	1	3.1	3	9.4	14	43.8	6	18.8	8	25.0
Nepafenac 1 mg/ml	1	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0
Nepafenac Vehicle	20	0	0.0	0	0.0	2	10.0	13	65.0	1	5.0	4	20.0

- Adverse events (AE)

The most frequently reported adverse events (related and not related combined) within patients with exposure to nepafenac 1 mg/ml Eye Drops, Suspension across all topical ocular clinical trials (N=832) were reduced visual acuity (3.5%), headache (3.5%), foreign body sensation in eyes (1.8%), conjunctival oedema (1.8%) and posterior capsule opacification (1.7%).

All other adverse events occurred at an incidence of 1.3% or less.

Table 11

Most Common Adverse Events - All Topical Ocular Clinical Studies
(C-95-91, C-95-92, C-95-93, C-96-08, C-97-30, C-97-52, C-00-35, C-00-60, C-00-61, C-02-53, C-03-32, C-04-08, C-04-41, C-04-65, C-05-08, and C-05-19)

Treatment	Nepafenac 3 mg/ml N=141		Nepafenac 1 mg/ml N=832		Nepafenac 0.3 mg/ml N=127		Nepafenac 0.1 mg/ml N=41		Nepafenac 0.03 mg/ml N=40		Ketorolac 5 mg/ml N=73		Ketorolac 4 mg/ml n=163		Diclofenac 1 mg/ml N=44		Nepafenac Vehicle N=549	
Coded Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
OCULAR																		
Visual Acuity Reduced	3	2.1	29	3.5	2	1.6	1	2.4			4	5.5	4	2.5			21	3.8
Foreign Body Sensation In Eyes	10	7.1	15	1.8	3	2.4	1	2.4	1	2.5			1	0.6			18	3.3
Conjunctival Oedema	1	0.7	15	1.8	2	1.6					4	5.5	8	4.9			17	3.1
Photophobia	1	0.7	5	0.6	1	0.8					1	1.4					24	4.4
Conjunctival Hyperaemia	3	2.1	3	0.4	4	3.1					1	1.4					19	3.5
Eye Pruritus	2	1.4	11	1.3	2	1.6	1	2.4	2	5.0			1	0.6			9	1.6
Eye Pain	2	1.4	4	0.5	2	1.6			2	5.0			4	2.5			9	1.6
Macular Oedema	2	1.4	1	0.1	2	1.6							3	1.8			8	1.5
Lacrimation Increased	2	1.4	3	0.4	4	3.1							1	0.6			5	0.9
Corneal Oedema	1	0.7	3	0.4	3	2.4					1	1.4					4	0.7
Vision Blurred	2	1.4	6	0.7	2	1.6	1	2.4									5	0.9
Vitreous Detachment	2	1.4	7	0.8	2	1.6											1	0.2
Vitreous Floaters	5	3.5	4	0.5	1	0.8											2	0.4
Eye Irritation	1	0.7	2	0.2					1	2.5			1	0.6	2	4.5	3	0.5
Ocular Hyperaemia	1	0.7			2	1.6											8	1.5
Asthenopia	1	0.7	2	0.2					1	2.5			1	0.6				
Posterior Capsule Opacification			14	1.7													12	2.2
Ciliary Hyperaemia			3	0.4							2	2.7	3	1.8			8	1.5
Corneal Striae			1	0.1	2	1.6											5	0.9
Eye Discharge	1	0.7	3	0.4	1	0.8			1	2.5							1	0.2
Visual Disturbance	1	0.7	1	0.1					1	2.5							1	0.2
NONOCULAR																		
<u>Infections And Infestations</u>																		
Nasopharyngitis	1	0.7	5	0.6									3	1.8			1	0.2
Influenza	1	0.7	1	0.1	2	1.6							1	0.6	1	2.3	2	0.4
Gastroenteritis	1	0.7													1	2.3		
Sinusitis			3	0.4	2	1.6												
<u>Injury, Poisoning, and Procedural Complications</u>																		
Injury	2	1.4	4	0.5	1	0.8							2	1.2	1	2.3	2	0.4
<u>Investigations</u>																		
Blood Potassium Increased	3	2.1																
Intraocular Pressure Increased			6	0.7	4	3.1			1	2.5	2	2.7					4	0.7
<u>Musculoskeletal And Connective Tissues Disorders</u>																		
Back Pain			2	0.2	1	0.8			1	2.5			3	1.8				
<u>Nervous System Disorders</u>																		
Headache	5	3.5	29	3.5					3	7.5			8	4.9			11	2.0
<u>Renal And Urinary Disorders</u>																		
Chromaturia							1	2.4										
<u>Skin And Subcutaneous Tissue Disorders</u>																		
Pruritus Generalised									1	2.5								
<u>Surgical And Medical Procedures</u>																		
Eye Laser Surgery			1	0.1									3	1.8				

Most common adverse events represent all events (related and not related combined) occurring at an incidence greater than 1.4% in any treatment group.

Ocular adverse events refer to adverse events coded into the MedDRA SOC Eye Disorders.

Nonocular adverse events are listed according to MedDRA SOC.

Foreign body sensation and eye pruritus appeared to occur with a slightly higher incidence in the nepafenac groups compared to the active comparator groups.

Blurred vision, vitreous detachment, vitreous floaters, ocular hyperemia, posterior capsule opacification and corneal striae occurred with incidences up to 3.5% in the nepafenac groups and generally with slightly lower incidences, in the vehicle group but not in the active comparator groups. However, patient numbers in these groups are low. Conjunctival edema occurred with a slightly higher incidence in the ketorolac groups.

No dose-relationship was observed for AE in the nepafenac groups.

The most frequently reported treatment-related adverse events in the population of patients participating in the post-cataract studies with exposure to nepafenac 1 mg/ml Eye Drops, Suspension

(N=728) were eyelid margin crusting (0.5%), eye pain (0.3%), and foreign body sensation (0.3%). Single treatment-related occurrences of iritis, conjunctival hyperemia, lacrimation increased, eye discharge, nausea, hypersensitivity and cutis laxa also were observed.

Table 12

**Most Common Adverse Events - Post-Cataract Inflammation Studies
(C-95-93, C-97-30, C-02-53, C-03-32, C-04-41, and C-04-65)**

Treatment	Nepafenac 3 mg/ml N=68		Nepafenac 1 mg/ml N=728		Nepafenac 0.3 mg/ml N=107		Nepafenac 0.1 mg/ml N=41		Nepafenac 0.03 mg/ml N=40		Ketorolac 5 mg/ml N=73		Ketorolac 4 mg/ml N=134		Nepafenac Vehicle N=487	
Coded Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
OCULAR																
Conjunctival Oedema	1	1.5	15	2.1	2	1.9					4	5.5	8	6.0	17	3.5
Foreign Body Sensation In Eyes	8	11.8	14	1.9	3	2.8	1	2.4	1	2.5			1	0.7	17	3.5
Photophobia	1	1.5	4	0.5							1	1.4			24	4.9
Conjunctival Hyperaemia	2	2.9	3	0.4	4	3.7					1	1.4			18	3.7
Eye Pruritus	1	1.5	8	1.1	2	1.9	1	2.4	2	5.0					9	1.8
Corneal Oedema	1	1.5	3	0.4	3	2.8					1	1.4			4	0.8
Vitreous Floaters	2	2.9	4	0.5	1	0.9									2	0.4
Reduced Visual Acuity			29	4.0	2	1.9	1	2.4			4	5.5	4	3.0	21	4.3
Posterior Capsule Opacification			14	1.9											12	2.5
Eye Pain			2	0.3	2	1.9			2	5.0			4	3.0	9	1.8
Ciliary Hyperaemia			3	0.4							2	2.7	3	2.2	8	1.6
Increased Lacrimation			2	0.3	4	3.7							1	0.7	4	0.8
Macular Oedema			1	0.1	2	1.9							3	2.2	5	1.0
Vitreous Detachment			7	1.0	2	1.9									1	0.2
Vision Blurred			2	0.3	2	1.9	1	2.4							4	0.8
Corneal Striae			1	0.1	2	1.9									5	1.0
Eye Discharge			3	0.4	1	0.9			1	2.5					1	0.2
Asthenopia			1	0.1					1	2.5			1	0.7		
Visual Disturbance			1	0.1					1	2.5						
Eye Irritation									1	2.5			1	0.7	3	0.6

The safety profile of nepafenac does not appear to be relevantly different from placebo (vehicle of nepafenac) or ketorolac. This holds true for both the overall population and the claimed target population. Only the higher concentration of nepafenac appears to show a numerically increased incidence of particular AE (namely foreign body sensation and vitreous floaters); however, the number of patients treated is too low.

Specific ophthalmologic assessments

Visual acuity and intraocular pressure

Several safety parameters have been represented over time, including IOP and VA. The effect on corneal thickness, endothelial cell counts and pupil diameter were based on data from a limited number of patients, so that no valid conclusion can be reached.

An assessment of the changes from baseline in optic nerve, retina/macula and choroids showed no deleterious effect on optic nerve following treatment with nepafenac as well as minor changes in the proportion of patients with evidence of active retina/macula and/or choroids inflammation. Similar conclusions apply for the remaining ocular safety parameters, including visual acuity which tended to increase over time in the majority of patients.

A review of the data showing the changes in IOP following surgery indicate that overall, mean changes were of minor relevance, followed the surgical procedure and tended to normalise over time (on D3), which is quite reassuring. Even though this observation was similar among treatments, and the surgical procedure instead of the anti-inflammatory therapies appears responsible for the observed changes in IOP, in order to properly assess its relevance, an analysis of the incidence of patients with clinically relevant changes in IOP, using a stricter criteria, was considered to be necessary.

The requested reanalysis of the changes in IOP using more stringent criteria (IOP \geq 24 mmHg at any visit) has been provided by the applicant. The incidence of patients in the nepafenac 1 mg/ml treatment group with IOP \geq 24 mmHg at any visit were slightly higher than those seen in the ketorolac 5 mg/ml and Vehicle treatment groups, but lower than those seen in the ketorolac 4mg/ml. In addition,

all adverse events reported for increased IOP were not related to study drug and did not interrupt patient continuation in the study. All treatment groups demonstrated a transient increase in IOP at Day 1 that returned to baseline by Day 3, which is commonly seen post cataract surgery.

Other ocular examinations

No differences between nepafenac and vehicle were found in the assessment of a number of additional ocular examinations (dilated fundus examination, pupil diameter and pupillary response, mean corneal thickness (pachymetry), endothelial cell density)

Cardiovascular examinations

Blood pressure and heart rate were assessed in 5 clinical studies (C-00-35, C-00-60, C-00-61, C-04-08, C-05-08), none of them in the claimed indication. Overall, data on 90 patients and healthy volunteers are provided, 27 of them aged 65 or older. Thirty nine of these subjects were treated with 3mg/ml, 24 with 1 mg/ml and 27 with vehicle. No differences in heart rate or blood pressure were observed between groups. Data on cardiovascular findings are scarce and of limited value. Admittedly, no major cardiovascular safety concern is expected from an NSAID topically administered short-term at such low doses.

• Serious adverse event/deaths/other significant events

Twenty-three serious adverse events were reported in 17 patients, including 3 patients (2.1%) with exposure to nepafenac 3 mg/ml, 5 patients (0.6%) with exposure to nepafenac 1 mg/ml, 1 patient (0.8%) with exposure to nepafenac 0.3 mg/ml, 1 patient (0.6%) with exposure to ketorolac 4 mg/ml, and 7 patients (1.3%) with exposure to nepafenac vehicle.

One patient among (on nepafenac 3mg/ml) experienced 2 serious adverse events (ulcerative keratitis and uveitis) following approximately 6 months of therapy that were assessed as related to therapy. This was the only patient on active therapy to experience serious adverse events that were ocular in nature. The types of non-ocular serious adverse events that were observed are not unexpected for an aging population.

Table 13

Other Serious Adverse Events - All Clinical Studies
(C-95-91, C-95-92, C-95-93, C-96-08, C-97-30, C-97-52, C-00-35, C-00-60, C-00-61, C-02-53, C-03-32, C-04-08, C-04-41, C-04-65, C-05-08, and C-05-19)

Patient ID	Treatment	Coded Adverse Event	Outcome of Event	Causality Assessment	DC Due to AE
C0061.2855.0307	Nepafenac 3 mg/ml	Ulcerative Keratitis	Resolved w/Tx	Related	No
		Uveitis	Resolved w/Tx	Related	No
C0253.1405.1303	Nepafenac 1 mg/ml	Aphasia	Continuing wo/Tx	Not Related	Yes
C0441.3747.0825	Nepafenac 1 mg/ml	Injury	Resolved w/Tx	Not Related	Yes
C0441.3828.0728	Ketorolac 4 mg/ml	Bradycardia	Resolved wo/Tx	Not Related	Yes
C9730.1007.0927	Nepafenac Vehicle	Uveitis	Resolved w/Tx	Not Related	Yes
C0035.2801.0205	Nepafenac 3 mg/ml	Hypoglycaemia	Continuing w/Tx	Not Related	No
C0035.2958.0118	Nepafenac 3 mg/ml	Hyperglycaemia	Resolved w/Tx	Not Related	No
C9593.1806.1614	Nepafenac 1 mg/ml	Gastritis	Resolved w/Tx	Not Related	No
		Nausea	Resolved w/Tx	Not Related	No
		Vomiting	Resolved w/Tx	Not Related	No
C9593.1806.1623	Nepafenac 1 mg/ml	Decreased Weight	Resolved w/Tx	Not Related	No
		Intestinal Obstruction	Resolved w/Tx	Not Related	No
		Bacterial Arthritis	Resolved w/Tx	Not Related	No
C0441.3807.1006	Nepafenac 1 mg/ml	Intestinal Obstruction	Resolved w/Tx	Not Related	No
C9593.1806.1653	Nepafenac 0.3 mg/ml	Pancreatitis	Resolved w/Tx	Not Related	No
C9593.1971.0423	Nepafenac Vehicle	Hypopyon	Resolved w/Tx	Not Related	No
C0035.2801.0204	Nepafenac Vehicle	Hypoglycaemia	Resolved w/Tx	Not Related	No
C0035.2958.0101	Nepafenac Vehicle	Hypoglycaemia	Resolved w/Tx	Not Related	No
		Anaemia	Continuing w/Tx	Not Related	No
C0332.2678.1712	Nepafenac Vehicle	Encephalitis Viral	Resolved w/Tx	Not Related	No
C0465.2804.1602	Nepafenac Vehicle	Diabetes Mellitus Inadequate Control	Resolved w/Tx	Not Related	No
C0465.3546.2012	Nepafenac Vehicle	Retinal Vein Occlusion	Continuing w/Tx	Not Related	No

Patient ID = Protocol number.Investigator number.Patient number w/Tx = with treatment wo/Tx = without treatment

DC Due to AE = Patient discontinued study participation due to the adverse event.

Table 2.7.4.2.1.3.-1 is sorted (in the following order) by (1) causality, (2) discontinuation due to event, (3) treatment, (4) protocol, (5) investigator, and (6) patient.

C0441.1204.501 with exposure to Ketorolac 4 mg/ml Eye Drops, Solution experienced a fatal serious adverse event not related to therapy and is presented in Table 2.7.4.2.1.2.-1.

One patient with exposure to ketorolac 4 mg/ml Eye Drops, Solution experienced a fatal adverse event (pneumococcal pneumonia) not related to therapy.

- Laboratory findings

Laboratory evaluations were performed in 1 macular edema study (C-00-35) and 2 pharmacokinetic studies (C-04-08 and C-05-08) with healthy volunteers involving topical ophthalmic dosing. Study C-00-35 involved a small sample size of patients who were dosed TID with either nepafenac 3 mg/ml (N=13) or nepafenac Vehicle (N=12) for up to 12 weeks. Laboratory test results were evaluated for patients at baseline (Eligibility), Week 12 (End-of- Treatment), and Week 20 (Exit). An analysis of the laboratory data (haematology, blood chemistry, and urinalysis) revealed no safety issues

Since the MAA submission, a post-cataract clinical study C-05-54 was completed that assessed clinical laboratory data in an additional Japanese 107 patients exposed to nepafenac 1 mg/ml Eye Drops. The additional laboratory data revealed no clinically relevant changes in laboratory parameters (haematology, blood chemistry, and urinalysis). Considering the PK and PD profile of nepafenac/amfenac, the potential for ethnic differences is unlikely and therefore, this information serves to support the previous conclusion on the laboratory safety profile of nepafenac.

- Safety in special populations

An analysis of adverse events was performed based upon various intrinsic factors (age, gender, race, iris colour, concomitant diseases, concomitant medications, and time of adverse event onset) in the population of patients in the post-cataract inflammation studies. No safety issues among patients receiving nepafenac 1 mg/ml were revealed.

Similarly, the safety evaluation of nepafenac in patients harbouring a number of different concomitant illnesses (e.g. glaucoma, DM, hypertension, GI disorders) have not shown any relevant safety finding.

- Safety related to drug-drug interactions and other interactions

Patients were allowed the use of concomitant medications not specifically prohibited by the protocol over the course of each study. Numerous concomitant medications were used by patients participating in the post-cataract inflammation studies (C-95-93, C-97-30, C-02-53, C-03-32, C-04-41, and C-04-65).

The occurrence of adverse events was analysed based upon patients' use of various concomitant medications: antihistamine drugs, anti-infective agents, anticholinergic agents, sympathomimetic (adrenergic) agents, cardiovascular drugs, antilipemic agents, central nervous system agents, analgesics and antipyretics, psychotherapeutic agents, EENT (eye, ear, nose and throat) preparations, gastrointestinal drugs, hormones and synthetic substitutes, antidiabetic agents, thyroid and anti-thyroid agents.

Adverse events did not occur with higher frequencies in the group of patients treated nepafenac 1mg/ml using any of above mentioned concomitant treatments, compared to the overall population treated with nepafenac 1mg/ml or with vehicle in the post-cataract inflammation studies

In order to further assess the safety of administering nepafenac 1 mg/ml in conjunction with other topical ophthalmic medications, an analysis was performed comparing the incidence of adverse events in patients receiving any topical ocular medication at any time during the study to the incidence of adverse events for all patients that received subgroups of topical ocular medications (i.e., antibiotics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics and mydriatics) anytime during the study. These analyses were confined to the pivotal cataract studies only.

Even though, no firm conclusions on the possible risk of local drug interactions can be drawn; the data provided show that most patients received additional topical ocular drugs according to clinical practice and in this setting the incidence of treatment related AE was almost nil, which is quite reassuring.

Patients with ocular prostaglandin analogues use were systematically excluded from clinical trials, and a statement has been added in the SPC (section 4.4) to reflect this.

- Discontinuation due to adverse events

Four patients discontinued study participation due to an unrelated serious adverse event (2 patients (0.2%) with exposure to nepafenac 1 mg/ml, 1 patient (1.4%) with exposure to ketorolac 4 mg/ml, and 1 patient (0.2%) with exposure to nepafenac Vehicle).

Thirty-five patients overall discontinued study participation due to nonfatal adverse events. Most AE that led to discontinuation were regarded as not related. Those 12 patients discontinuing due to treatment related AE recorded the following AE:

nepafenac 1mg/ml; allergic conjunctivitis, choroidal effusion, keratitis, corneal deposits ketorolac 5mg/ml: conjunctival hyperaemia

Nepafenac vehicle; eye pain and photophobia, corneal oedema in 2 patients, iritis, conjunctival oedema and allergic conjunctivitis, ciliary hyperemia, hypersensitivity.

- Post marketing experience

Nepafenac 1 mg/ml Eye Drops, Suspension, is registered in the United States as NEVANAC (nepafenac ophthalmic suspension) 0.1% and received marketing authorization on 19 August 2005 for the indication; treatment of pain and inflammation associated with cataract surgery.

In the time period between 19 August 2005 and 30 September 2006, 111 spontaneous adverse event reports encompassing 217 reaction terms were received. Overall, most adverse reactions were reported in patients treated as prophylaxis following refractive surgical procedures.

Twenty reports were classified as serious and associated with refractive surgery cases (15 reports: 7 LASIK procedures; 5 PRK procedures; 3 unspecified procedures), cataract cases (2 reports) and 1 case each of corneal transplant, dry eye/allergy and cystoid macular oedema.

Based on the number of units sold (545,127) during this time interval, the overall incidence of spontaneous reports since initial marketing authorisation is approximately 0.02%.

- Discussion on clinical safety

One hundred sixty-six patients have been exposed to nepafenac 1mg/ml Eye Drops for at least 21 days. Even though the vast majority of patients were treated for a shorter duration, these data add reassurance and support the maximum recommended duration of the treatment.

The safety profile of nepafenac does not appear to be relevantly different from placebo (vehicle of nepafenac) or ketorolac. This holds true for both the overall population and the claimed target population. Only the higher concentration of nepafenac appears to show a numerically increased incidence of particular AE (namely foreign body sensation and vitreous floaters). However, the number of patients treated is too low. Serious AE were infrequent.

No safety issues were identified based upon an analysis of visual acuity, IOP and other ocular examinations, but the provision of plots (with confidence intervals) of the ocular examinations are requested.

Data on cardiovascular findings are scarce and of limited value. Admittedly, no major cardiovascular safety concern is expected from an NSAID topically administered short-term at such low doses.

There is no evidence for any relevant laboratory abnormalities that would be expected from a NSAID to be administered topically.

The safety of nepafenac when co-administered with a wide variety of drugs (e.g. antihistamine, anticholinergic agents, sympathomimetic, analgesics and antipyretics) did not reveal specific safety concerns.

Even though, no firm conclusions can be drawn on the possible risk of local drug interactions with other ophthalmic medications such as antibiotics, anesthetics, betablockers, carbonic anhydrase

inhibitors, alpha-agonists, cycloplegics, and mydriatics, the data provided show that most patients received additional topical ocular drugs according to clinical practice and in this setting the incidence of treatment related AE was almost nil, which is quite reassuring.

Patients with ocular prostaglandin analogues use were systematically excluded from clinical trials, and a statement has been added in the SPC (section 4.4) to reflect this.

The formulation intended for marketing utilized benzalkonium chloride as a preservative solution. The use of contact lenses should be avoided during treatment with nepafenac and is mentioned in the SPC (section 4.4).

No safety concerns have been raised from the post-marketing safety data but the information is still limited.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table 14 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Safety concern Corneal disorders	<ul style="list-style-type: none">▪ routine pharmacovigilance▪ no additional activity is proposed at this time	None at this time.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are appropriate for an ophthalmic preparation. The results of the tests indicate that the active substance and the finished product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

Non-clinical pharmacology and toxicology

Overall, adequate non-clinical pharmacology and toxicology data have been provided by the applicant.

Efficacy

A complete clinical development plan, aimed to demonstrate superiority over placebo and non-inferiority over an active comparator have been performed. These studies show that nepafenac, given at 1mg/ml TID starting the day before surgery and up to 4 weeks after surgery, has an ocular anti-inflammatory effect superior to placebo and, although the magnitude of the effect is not impressive, it is similar to that seen with other currently authorised products of the same family (NSAIDs).

Duration of the treatment for up to 3 weeks in the postoperative period after starting one day prior to surgery is recommended in the Posology section (4.2) of the SPC. However, final evaluation of the treatment duration showed that 14 days treatment should be recommended, although could be extended for up to 3 weeks based on physician's judgement.

Plausible evidence for efficacy of the nepafenac eye drops 0.1 % suspension in the revised therapeutic indication has been presented in the dossier.

Safety

The safety profile of nepafenac does not appear to be relevantly different from placebo (vehicle of nepafenac) or the active comparator ketorolac. This holds true for both the overall population and the claimed target population. Serious AE were infrequent and none of them considered related to the study drug.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- **User consultation**

Alcon Laboratories (U.K.) Limited provided a user testing report on NEVANAC (nepafenac) used to the prevention and treatment of pain and inflammation associated with cataract surgery.

Methodology

The test was designed to be performed in two rounds of face-to-face interviews. Before the first round was conducted, a pilot set questionnaire of fourteen test questions was performed and consequently, the questions were re-worded and re-designed by Consumption, based on the key issues associated with NEVANAC.

The interviews were conducted by an experienced interviewer and took no longer than 45 minutes in duration (to avoid tiring participants) which is considered acceptable.

With regards to the time aspects, omitting a reading phase prior to the interview simulates a "real life situation" very well. Users of the medicine are more likely to be searching directly for specific answers in the leaflet than to be reading it from a to z and then start looking for answers. This approach adds strength to the present user testing.

Population

The population recruited was 20 subjects in 2 stages, the first round (including 10 subjects) and the second round (including other 10 subjects).

The number of subjects included on the user testing is considered sufficient according to the European requirements. ("Guideline on the readability of the label and package leaflet of medicinal products for human use" Revision September 2006)

Participants were recruited using a professional recruiter. The report does not mention how the participants were recruited. The report does not mention any exclusion criteria (for instance, people with medical training) nor does the report mention any inclusion criteria. Nevertheless, the participants are considered acceptable:

- All the subjects were healthy volunteers (no familiarisation time was allowed before interviews began) , wearing a patch over one eye to simulate less than perfect vision, since this product is indicated to prevent and relieve eye pain and inflammation following a cataract surgery on the eye.
- The range of age used by the applicant was people aged from 46 to 67. Due to the fact that the cataract surgery could be carried out over an age of 67, the applicant could have chosen some people over 67.
- Both genders were included in a balanced manner (60% female and 40% male)

- Educational level of tested population is considered well balanced since covered different social groups using a system of classification widely used in social research.

Questionnaire

The number of questions included in the questionnaire is considered sufficient.

The Applicant has provided fourteen questions for the interviews related to sections 1 to 5 of the Package Leaflet, including the instructions for use.

Although the report do not describe which areas in the leaflet were chosen as important areas to be tested, we consider that the battery of questions covers all the important key-points in the leaflet and are presented in a random order, which is considered acceptable. Therefore, the proposed questionnaire is considered acceptable.

Results

The applicant recorded an answer as correct when the participants had achieved 3 criteria: that they can find, understand and use the information.

Overall results on the NEVANAC 1 mg/ml eye drops, suspension shows that;

- 95.7% of the interviewees correctly located the information, which is considered acceptable.
- 94.6% of the interviewees correctly answered the question, which is considered acceptable.

Conclusions

Considering the design, population, questionnaire and results provided by the Applicant of NEVANAC 1 mg/ml eye drops, suspension, the CHMP considers this User Testing acceptable.

Due to the fact that the percentage of adequate results obtained in almost all the questions are above 90% no changes have been implemented, although, different areas of potential improvement have been detected.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of NEVANAC in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery was favourable and therefore recommended the granting of the marketing authorisation.