Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for nepafenac

Proprietary Product Name: Ilevro

Sponsor: Alcon Laboratories (Australia) Pty Ltd

December 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
ASA	Australian Specific Annex
AUC	area under the plasma concentration time curve
BCVA	best corrected visual acuity
CL/F	apparent plasma clearance
Cmax	maximum plasma concentration
CSR	clinical safety report
LDPE	low density polyethylene
IC50	inhibitory concentration 50%
ICB	iris ciliary body
IOP	intraocular pressure
ISS	integrated summary of safety
NNT	number needed to treat
NSAID	non steroidal anti inflammatory drug
PD	pharmacodynamic
PI	Product Information
PK	pharmacokinetic
PSUR	periodic safety update report
RMP	Risk Management Plan
SAE	serious adverse event
SmPC	summary of product characteristics
$t_{1/2}$	half life
Tmax	time of maximum plasma concentration

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	3 November 2015
Date of entry onto ARTG	4 November 2015
Active ingredient:	Nepafenac
Product name:	Ilevro
Sponsor's name and address:	Alcon Laboratories (Australia) Pty Ltd 10/25 Frenchs Forest Road East Frenchs Forest NSW 2086
Dose form:	Eye Drops, suspension
Strength:	3 mg/mL (0.3%)
Container:	Low density polyethylene (LDPE) dropper bottle
Pack size:	3 mL
Approved therapeutic use:	The prevention and treatment of postoperative pain and inflammation associated with cataract surgery
Route of administration:	Ocular
Dosage:	1 drop once a day beginning 1 day prior to cataract surgery, continued on the day of surgery. In clinical studies, the effectiveness of Ilevro was demonstrated for up to 14 days of the postoperative period. Treatment durations greater than two weeks and a dosing frequency of more than once daily have not been assessed. An additional drop should be administered 30 to 120 minutes prior to surgery.
ARTG number (s):	230200

Product background

This AusPAR describes the application by Alcon Laboratories (Australia) Pty Ltd to register nepafenac (trade name, Ilevro) 0.3% eye drops. This product is a non steroidal anti inflammatory drug (NSAID) for topical application to the eye prior to and after cataract surgery.

Nepafenac Ophthalmic Suspension 0.3% has been developed as a reformulation of the overseas marketed Alcon product, Nevanac (Nepafenac Ophthalmic Suspension, 0.1%). The rationale for the reformulation was to develop a once-a-day product improving

convenience and dosing compliance for the patient while ensuring an efficacy and safety profile similar to or better than Nevanac.

Although it is a new chemical entity in Australia, a 0.1% strength product has been marketed from 2005 in over 60 countries. In the EU, the indication for the 0.1% nepafenac formulation is:

> *Nevanac 1 mg/ml is indicated in adults for:*
>
> - *Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.*
> - *Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.*

The 0.1% nepafenac eye drops require administration three times a day, while the 0.3% eye drops are proposed for once daily administration.

The 0.3% nepafenac formulation is not approved for reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients and this indication has not been proposed for Australia. The 0.3% solution was approved for marketing in the EU in May 2013, in the USA in October 2012 and in Canada in August 2013. The indications and dose regimen in the EU are the same as those proposed in this submission. There are minor differences in both the indications and duration of post operative use in the USA and Canada.

The sponsor has stated that based on the duration of action of amfenac being >24 h, a once a day product was developed to improve patient compliance and reduce treatment burden. The formulation of 0.1% product was modified including the addition of guar and carbomer 974P as viscosity agents to product a suspension dosage form.

Currently, there are no NSAID eye drops with a once a day dosing regimen registered and marketed in Australia for the proposed indication. Products currently available are Acular eye drops (ketorolac 5 mg/mL) and Voltaren Ophtha eye drops (diclofenac sodium 1mg/mL). These products are approved for the prevention and reduction in inflammation from cataract surgery and require the administration of up to 1 to 2 drops from 3 to 5 times daily. The 0.1% nepafenac eye drops have been available in Australia since 2009 and the sponsor has advised that will cease should the nepafenac 0.3% eye drops be registered.

Fenazox, an oral formulation of amfenac, is available in Japan for pain relief and its anti inflammatory effect post operatively, external injury, tooth extraction, chronic rheumatoid arthritis, osteoarthritis and low back pain. Fenazox is dosed in 50 mg increments to a maximum of 200 mg per day, in four divided doses.

Regulatory status

At the time of submission to TGA, Ilevro had been approved for similar indications in the US (October 2012), EU (May 2013) and Canada (August 2013). Similar applications were intended for submission to New Zealand (October 2014), Switzerland (late 2014) and Singapore (2016).

Product information

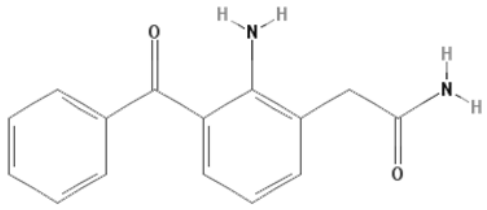
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

The structure of nepafenac is shown in Figure 1.

Figure 1: Chemical structure of nepafenac.



Nepafenac is a member of the NSAIDs. NSAIDs are used pre and post cataract surgery to minimise the magnitude and duration of the inflammatory response resulting from surgical trauma.

Nepafenac (amfenac amide) is a pro drug which is converted to amfenac by intraocular hydrolases. Nepafenac is formulated as a suspension applied by the topical ocular route, and it is indicated for the prevention and treatment of pain and inflammation associated with cataract surgery.

Drug substance (active ingredient)

Table 1 details the general properties of nepafenac.

Table 1: General chemical properties of nepafenac.

ANN/BAN/INN/USAN	Nepafenac
Chemical name(s):	2-(2-Amino-3-benzoylphenyl)acetamid (IUPAC) 2-(2-Amino-3-benzoylphenyl)acetamide (WHO) 2-Amino-3-benzoylbenzeneacetamide (USAN)
Molecular formula	$C_{15}H_{14}N_2O_2$
Molecular weight	254.28
CAS number	78281-72-8
Appearance	Nepafenac drug substance is provided as a yellow crystalline or powder material
Solution colour and clarity	A 0.5 mg/mL solution of nepafenac in acetonitrile is yellow and clear (colour NMT Ph. Eur GY2 and clarity NMT Ph. Eur I).
Solubility	**Solvent** / **Solubility (mg/mL)** Methanol 3.68 Acetonitrile 3.26 Chloroform 1.66 1-Octanol 0.62 Toluene 0.06 Water 0.014
Melting point	184.0°C to 184.9°C.
Specific Rotation	Nepafenac is an achiral substance and there are no possible variations in the stereochemical configuration.
Solution pH	The pH of a 1% suspension of nepafenac is 6.75
Dissociation Constants	Nepafenac drug substance has a solubility of less than 14 ppm in water. Therefore, no meaningful measurement of dissociation constant can be obtained
Polymorphism	Nepafenac drug substance does not exhibit polymorphism.

The solid state stability of nepafenac drug substance was assessed with storage at 40°C/75% relative humidity (RH) for 26 weeks. The results showed no moisture uptake, no change in colour, assay values remained within 98.0% to 102.0%, and no formation of degradation products, indicating the drug substance in the solid state is stable.

The drug substance is stored in a colourless polyethylene bag. The bag is then wrapped in a second, identical polyethylene bag that is packed in a cardboard container. This is the same container used in stability studies. A Certificate of Analysis and IR spectrum was provided for the LDPE bags.

The finished product manufacturer has completed aqueous suspension and solid stress degradation studies, as well as the accelerated stability study at 40°C/75% RH (up to 26 weeks) and the study at normal storage conditions at 25°C/60% RH (up to 5 years). The stress studies and the accelerated study have demonstrated that nepafenac is stable, is not hygroscopic or sensitive to light degradation.

The results reported for each batch were within the proposed limits for each parameter throughout the stability studies conducted at 25°C/60% RH in the proposed container closure system with the exception of the Assay measured at the 78 week test station.

An investigation was performed which revealed that the variable or out of specification assay results were due to flaws in the sample preparation procedure. The procedure was updated to increase the amount of sample weighed and increase the volumes used for the final dilution of samples. The improved method was subsequently shown to be a more robust method for the Assay.

The data provided support the proposed retest date of 5 years for the drug substance stored at 25°C/60% RH in the proposed container closure system.

Drug product

Nepafenac 3 mg/mL Eye Drops Suspension is a sterile, preserved, stable, multi-dose aqueous light yellow to yellow uniform suspension formulated for topical ophthalmic application.

Optimisation studies were conducted to evaluate characteristics such as suspension behaviour (settling and resuspendability), viscosity, pH, tonicity and preservative effectiveness. Rabbit topical ocular bioavailability studies were also conducted to determine the effect of different formulations on bioavailability.

During development the key physiochemical characteristics relevant for the product performance (particle size, polymorphism and uniformity/homogeneity of dose) were identified and analysed appropriately.

Compatibility of the drug substance and the excipients in the proposed container system has been evaluated. A stability study conducted on two lots of 0.3% nepafenac eye drops suspension filled in LDPE bottles did not show significant changes in the physical, chemical and microbiological characteristics of the formulation at the long term (25 °C/40% RH for 56 weeks) and accelerated (40 °C/<25% RH for 26 weeks) storage conditions.

The data obtained in this study supports the compatibility of the excipients used in the formulation and the appropriateness of the packaging used for the conditions studied.

The proposed 'Drop-Tainer' package system has previously been approved as part of Alcon's Simbrinza (Brimonidine tartrate & brinzolamide eye drop suspension) and Azarga (Brinzolamide and Timolol [as the Maleate]).

The Dupont 20-6064 LDPE resin used in the bottle contains polyethylene glycol and therefore does not comply with European Pharmacopoeia (Ph. Eur.) 3.1.4. Alcon however

have tested all resins used for the primary packaging and confirmed that they comply with Ph. Eur. 3.1.4 (LDPE), 3.1.6 (PP), USP General Chapter <661>, <87> and <88> and ISO Guidelines for packaging components sterilised by ethylene oxide or gamma irradiation (ISO 11135-1:2007[1] and ISO 11137-1:2012[2]).

The suppliers of the polypropylene used in the closure confirmed the material's compliance also with Ph. Eur. General Monograph 3.1.3 Polyolefins.

Leachables/extractables studies

Extractable studies have been performed on components for the proposed container closure system. Containers were filled with pH 3 and pH 9 buffered saline and stored for 7 days at 60°C and for 12 weeks at 40°C. Additionally, container material was finely shredded and stored for 7 days at 60°C in both pH 3 and pH 9 buffered saline. The resulting solutions were tested for extractable material using gas chromatography (polar and nonpolar) and by HPLC.

A leachables study was also conducted on components for the proposed container closure system. Samples were stored at the stressed conditions of 70°C for 24 h.

No extraneous peaks were found by HPLC. Several extraneous peaks, with concentrations ranging from 0.2 to 1.3 ppm, were found by gas chromatography. These concentrations are below the threshold of toxicological concern of 1.5 µg/day stated in published guidelines.[3]

The performance of the container closure system was assessed by a drop size study to assess drop uniformity. The results demonstrate adequate uniformity of the delivered drug product with an average drop size of approximately 53 µL ± 6.4 µL.

Stability

Three primary batches (11D05Y, 11D08J and 11F27Q) of nepafenac 3 mg/ml eye drops, suspension were manufactured at the Alcon-Couvreur Manufacturing Facility in Belgium. A further three supportive lots were compounded according to the proposed manufacturing procedures (two at Alcon's Process Development building and one at Alcon's ASPEX manufacturing building, both sites located in the US).

A shelf life of 78 weeks shelf life is proposed for the nepafenac 3 mg/mL Eye Drops Suspension filled to 3 mL in LDPE bottles when stored at not more than 25°C and protected from light. A shelf life after opening of product of 28 days is proposed.

The stability data submitted adequately support the proposed shelf life of 18 months when stored at not more than 25°C and protected from light.

The results for in-use stability testing of Nepafenac 3 mg/ml Eye Drops, Suspension support the proposed in-use period of 28 days.

Biopharmaceutics

In accordance with the TGA's 'Guidance 15: Biopharmaceutic studies', under 'Medicines that do not require biopharmaceutic data', no bioavailability study has been included with the application as the proposed product falls under the criteria of 'Medicines containing drug substances that are not systemically or locally absorbed'.

[1] ISO 11135 EtO Sterilisation for Medical Devices
[2] ISO 11137 Gamma & E-Beam Sterilization for Medical Devices
[3] European Medicines Agency, "Guideline of the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006)", 28 June 2006.

To support their justification for not providing appropriate biopharmaceutic studies, the company included results from a Phase I study (C-09-053) to assess the systemic pharmacokinetics of nepafenac and its pharmacologically active metabolite amfenac.

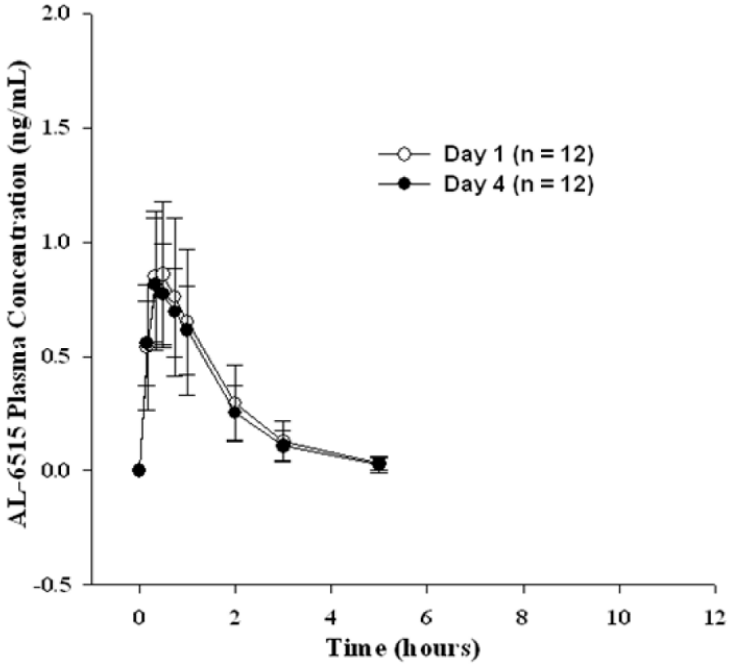
Study C-09-053 was a single centre, multiple dose, double masked, randomised, parallel group pharmacokinetic study. The primary objective of this study was to characterise systemic pharmacokinetics of nepafenac and its pharmacologically active metabolite amfenac after a single dose and at steady state following once daily topical ocular dosing of Nepafenac 0.3% for 4 days in healthy subjects.

Plasma samples were collected at 0 hour (pre dose), 0.17, 0.33, 0.5, 0.75, 1, 2, 3, 5, 8 and 12 hours on Day 1 and Day 4 over a 24 hour period.

Plasma concentrations of nepafenac and amfenac were determined using a validated HPLC-MS/MS method, with quantitation limits of 0.025 ng/mL for both nepafenac and amfenac, respectively. The pharmacokinetic parameters (Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ were estimated from the plasma concentrations of nepafenac and amfenac using a non-compartmental analysis method.

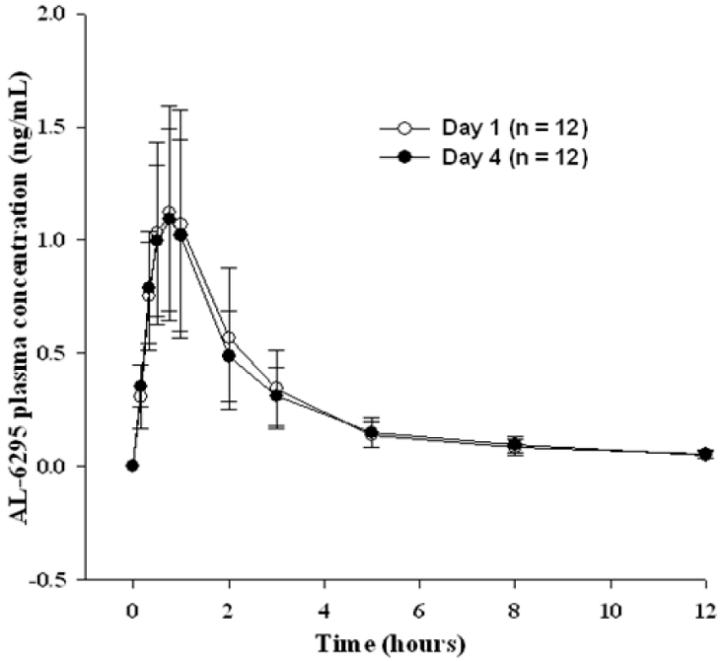
After single dosing of 1 drop of nepafenac 0.3% once daily for 4 days, the mean exposure (measured by AUC_{0-t}) of nepafenac was 1.50 ng*h/mL on Day 1 and 1.34 ng*h/mL on Day 4. The median $t_{1/2}$ of nepafenac was 0.85 h on Day 1 and 0.74 h on Day 4, and the mean AL-6515 plasma concentration was below the limit of quantitation at 8 h (of a 24 hour dosing interval) on Day 1 and Day 4. The plasma concentration versus time profiles on Day 1 and Day 4 were similar indicating a lack of accumulation (Figure 2).

Figure 2: Mean (± SD) AL-6515 plasma concentration versus time profiles on Day 1 and Day 4 after once daily bilateral topical ocular instillation of 1 drop of nepafenac 0.3% in 12 healthy subjects.



After single dosing of 1 drop of nepafenac 0.3% once daily for 4 days, the mean exposure (measured by AUC_{0-t}) of amfenac, was 3.28 ng*h/mL on Day 1 and 3.33 ng*h/mL on Day 4. The median $t_{1/2}$ of amfenac was 5.49 h on Day 1 and 6.26 h on Day 4, and the mean amfenac plasma concentration were Below the Limit of Quantitation (BLQ) at 24 h (of a 24 h dosing interval) on Day 1 and Day 4. The mean amfenac plasma concentration versus time profiles on Days 1 and 4 were similar indicating a lack of accumulation (Figure 3).

Figure 3: Mean (± SD) AL-6295 plasma concentration versus time profiles on Day 1 and Day 4 after once daily bilateral topical ocular instillation of 1 drop of nepafenac 0.3% in 12 healthy subjects.



Minimal or no plasma accumulation of nepafenac or amfenac were observed after topical ocular administration of nepafenac 0.3%. The information provided demonstrates that the proposed product satisfies the requirements of TGA's Guidance 15.

Quality summary and conclusions

The chemical, pharmaceutical and biopharmaceutic aspects of the application are complete and satisfactory except for the following deficiencies that require resolution before the product can be considered acceptable for registration in Australia:

Drug Substance

- The manufacturing process corresponds to Process C where the form of the 2-propylthioacetamide starting material is introduced to the reaction mixture as a suspension in toluene. Manufacturing Processes D and E have also been discussed where this starting material is introduced in the synthesis as solid material (see ASMF/DMF evaluation R15/260152).

  The manufacturer, therefore, should be asked to confirm that the manufacturing process for the drug substance to be used in the proposed Ilevro (nepafenac 0.3%) Eye Drops Suspension is Process C.

Drug product

- The assay must be reported to one decimal place. The manufacturere therefore should be asked to tighten the assay limits to 95.0-105.0%. Given there was very little difference observed in the assay over the long term stability studies, the manufacturer should also asked to tighten the shelf life limits to 95.0-105.0%.
- Given the antimicrobial effectiveness was demonstrated at 81% for benzalkonium chloride and 84% of label for EDTA, a shelf life specification of 85.0% to 115.0% would

be acceptable with the inclusion of one decimal place for each. The manufacturer to be asked to update the specification accordingly.

- The manufacturer is requested to provide the shelf life specification which includes the identification of nepafenac and identification tests for the preserving agents, benzalkonium chloride, and disodium edetate. This is required for regulatory purposes and it is not a requirement to perform these tests during stability studies.
- The observed particle size ranges for primary and supportive stability lots are similar to those of the clinical lot (18502-01), however, the manufacturer should also demonstrate that the drug product complies with the test and limit for larger particles specified in the British Pharmacopeia (Ph. Eur. 1163) Eye Preparations monograph.
- The manufacturer is asked to justify only storing the stability samples horizontally.
- The manufacturer is asked explain how the bottles used in the stability study cover the range of the proposed LDPE resins, dispensing plugs and closures.
- As discussed above, the assay results must be reported to one decimal place. The manufacturer is reminded that in future stability tests, the assay results must be reported to one decimal place.

III. Nonclinical findings

Introduction

Alcon Laboratories (Australia) Pty Ltd has applied to register a new chemical entity, nepafenac (Ilevro) for the treatment of post operative pain and inflammation following cataract surgery. Nepafenac was initially assessed by the Food and Drug Administration (FDA) as a 0.1% suspension, and then as the 0.3% formulation. The two FDA reports form the basis of this evaluation. Studies not considered by the FDA have been evaluated in the main body of this evaluation.

The dossier contained studies that addressed relevant International Conference on Harmonisation (ICH) guidelines. Toxicity studies were Good Laboratory Practice (GLP) compliant, but safety pharmacology studies of nepafenac were not. The summaries did not discuss the majority of studies, and appeared to have been written for a change in formulation rather than a new chemical entity.

Pharmacology

Primary pharmacology

Data from separate in vitro studies suggested that nepafenac was a pro drug metabolised to the pharmacologically active metabolite, amfenac (nepafenac and amfenac IC50 values for COX: 64 and 0.25 μM, respectively). However, as these data were generated in separate studies and minimal or no experimental detail or raw data were provided, it is unclear how comparable these values are. When compared directly in more recent studies, it was demonstrated that nepafenac had similar or greater inhibitory activity against COX-1 and COX-2 than amfenac (see Table 2). Nepafenac was a mixed inhibitor of COX-1 and COX-2 and inhibition was not time dependent. In contrast, amfenac was a time-dependent, competitive inhibitor of COX-1 and COX-2. Together, the new data indicate that both nepafenac and amfenac contribute to the pharmacological effects of Ilevro, and that nepafenac is not solely a pro-drug as early data suggested.

Table 2: Inhibition of COX isoforms by nepafenac and its active metabolite.

	COX-1		COX-2	
	IC_{50} (μM)	K_i (μM)	IC_{50} (μM)	K_i (μM)
Nepafenac	9.7	2.3-3.4	85	12
Amfenac	16.9	3.9-4.1	180	17-26

The permeation of nepafenac though rabbit cornea was greater and more rapid than amfenac and diclofenac (another NSAID indicated for topical ocular use). Greater permeation of nepafenac compared to diclofenac was also demonstrated in conjunctival and scleral tissues. The formulation of the vehicle affected that permeation of 0.1% nepafenac solutions, with reductions in Carbomer 974P concentration reducing permeation in the cornea by ~35%. Hydrolysis of nepafenac to amfenac occurs in cornea, iris ciliary body (ICB) and the retina/choroid. In rabbit tissue, the rate of hydrolysis was low in cornea (0.1-0.3 nmol/min/mg), moderate in ICB (0.2-0.7 nmol/min/mg) and highest in the retina/choroid (6 nmol/min/mg). In human tissue, the rate of hydrolysis was highest in the ICB (0.5 nmol/min/mg), and lower in the cornea and retina/choroid (0.1 nmol/min/mg).

Topical ocular administration of 0.1% nepafenac inhibited ex vivo prostaglandin synthesis in the ICB by up to 89%, with similar efficacy to amfenac. Similarly, 0.3% nepafenac also inhibited PGE2 synthesis in ICB tissue with no further effect of the vehicle. However, compared to the Nevanec vehicle, the proposed vehicle for Ilevro appeared to also inhibit PGE2 synthesis in ICB. In addition, topical ocular administration of ≥0.05% nepafenac inhibited PGE2 and total prostaglandin synthesis ex vivo in ICB and retina/choroid after 10 minutes, with maximal inhibition in ICB from 40 minutes post-application and 80 minutes in retina/choroid (inhibition ranged from 38-50%). In comparison, 0.1% diclofenac more rapidly and potently inhibited PGE2. In a separate ex vivo study, nepafenac inhibited PGE2 synthesis in ICB by ≥57% for up to 24 h. In vivo, topical nepafenac (0.01-0.1%) inhibited PGE2 synthesis and protein influx in response to trauma (paracentesis), with similar efficacy to amfenac and diclofenac. In a model of concanavalin A-induced pan retinal inflammation, topical ocular administration of 0.1-1% and 10 mg/kg SC nepafenac reduced retinal thickening and inhibited vitreal protein and PGE2 accumulation. The latter effects were not observed with ocular application of diclofenac and ketorolac.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamics studies assessed the interaction of 1-100 μM nepafenac with 21 receptors and binding sites, with no interactions identified. The receptor and binding sites tested included those for neurotransmitters, opioids, various peptides, growth factors, prostaglandins, steroid, second messenger and immunologic factors.

Topical ocular administration of nepafenac inhibited pre retinal neovascularisation in rodent models of oxygen induced retinopathy. Similarly, choroid neovascularisation was also inhibited by nepafenac in rodents and rabbits. Nepafenac also inhibited diabetes-induced increases in retinal PGE2 and superoxide protein levels, decreased retinal capillary apoptosis and pericyte ghosts, but did not affect retinal VEGF protein expression. Furthermore, nepafenac did not affect VEGF or diabetes induced retinal permeability in rodents and rabbits.

Some data were provided that indicated amfenac, but not nepafenac, inhibited proliferation and tube formation in bovine retinal endothelial cells. The sponsor suggested that the lack of effect observed with nepafenac may be due to a lack of metabolism to amfenac. However, other studies demonstrated high metabolism of nepafenac to amfenac in retina/choroid tissue, and other tissues tested. In addition, the newly provided data

indicate similar or greater COX inhibition with nepafenac compared to amfenac. The studies submitted containing these data had very little experimental information and no detailed data. Therefore, the effect of nepafenac on retinal endothelial cell proliferation and tube formation in vitro remains unclear.

Specialised safety pharmacology studies covered the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems, as well as corneal reflex. None of these studies were GLP compliant, which is inconsistent with recommendation in ICH guideline 7A. In addition, the effects of nepafenac on the cardiovascular system were inadequately addressed as no in vitro studies were submitted, as recommended by ICH guideline 7B. Two GLP compliant cardiovascular safety pharmacology studies were conducted with amfenac, the major nepafenac metabolite. There were no adverse effects of amfenac on the cardiovascular system at exposures of 88× clinical Cmax in an in vitro hERG channel study, and >10,000× in an in vivo dog study. Overall, while the safety pharmacology studies did not identify any specific risks of nepafenac, the cardiovascular effects of nepafenac have not been fully investigated and the lack of GLP compliance is a deficiency. However, the low systemic exposure following ocular administration decreases toxicological concern.

Pharmacokinetics

Absorption: Nepafenac was rapidly absorbed following topical ocular administration in rabbits and humans (Tmax 0.2-0.5 h), with moderate ocular bioavailability demonstrated in rabbits (48%). Similarly, the major metabolite, amfenac, was rapidly formed and absorbed following ocular dosing of nepafenac in rabbits. The increase in systemic exposure to nepafenac and amfenac following ocular dosing was generally less than dose proportional. The plasma half life of nepafenac and amfenac was mostly short (≤1 h) following oral, intravenous or topical ocular dosing in rats, rabbits, monkeys and humans. The exception was the plasma half life of amfenac in humans following topical ocular dosing, which was approximately 6 h. The half life of nepafenac in ocular tissues was biphasic, with $t_{1/2}\alpha$ ranging from 0.2-2 h in most ocular tissues except the lens where it was 11 h. $t_{1/2}\beta$ was generally longer, with values ranging from 2-49 h. Following a single topical ocular dose (30 µL, 0.3%) in rabbits, nepafenac and/or amfenac were generally detected after 24 hours in all ocular tissues.

Distribution: Plasma protein binding by nepafenac was moderate in humans (84%), rats (73%) and monkeys (80%). Higher serum binding was reported for amfenac in humans (99%), with high amfenac binding to human and rat albumin also demonstrated (95% and 98%, respectively).[4] Ocular distribution studies of nepafenac showed highest levels in the cornea and conjunctiva, with moderate distribution to the ICB and aqueous humour, and low levels observed in choroids, retina and lens. Following oral dosing, levels of nepafenac and/or its metabolites were highest in stomach, liver, kidneys and urinary bladder, with long tissue half-life.

Metabolism: The major metabolite, amfenac, was formed by hydrolysis. Following topical ocular dosing in rabbits, nepafenac was the predominant species with similar or lower levels of amfenac observed. In contrast, the predominant plasma species was amfenac after either oral or ocular dosing. In the eye, one unidentified metabolite was observed at low levels in the cornea, ICB and aqueous humour. Up to 12 metabolites of nepafenac were observed in vitro, with 10 observed in vivo, but only four were identified. These metabolites were formed by hydroxylation, cyclisation or a combination of these processes. Conjugation of metabolites with glucuronide was observed in monkeys and humans, but not rats. Amfenac was identified as the major metabolite in rats, rabbits,

[4] Kiso et al. Absorption, Metabolism and Excretion of Amfenac Sodium (I) – Absorption, Distribution and Excretion in Rats. *Clinical Report* 48: 29-41 (1984).

monkeys and humans, with a similar profile of identified metabolites in monkeys and humans. The similarity of other metabolites across species is unknown. The enzymes responsible for metabolism of nepafenac and/or amfenac were not assessed. Nepafenac and amfenac did not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4 enzymes in vitro. In SD rats, oral administration of 10 mg/kg/day nepafenac did not induce expression of CYP1A, 2B, 3A or 4A, and had minimal effect on enzyme activity.

Excretion: Metabolites of nepafenac were excreted predominantly in the urine (55-86%) after oral or IV dosing in rats, monkeys and humans. Moderate faecal excretion (40%) was observed in SD rats following IV dosing. Excretion routes were not assessed after topical ocular dosing.

Conclusion: The absorption, metabolism to amfenac, and half life of nepafenac was generally similar between laboratory animals and humans. The metabolic fate of nepafenac and/or amfenac was not fully defined in either humans or laboratory animals and therefore uncertainty remains in terms of the similarity in metabolite profile. Overall, the species used in nonclinical studies appear appropriate for examining toxicological effects of nepafenac.

Pharmacokinetic drug interactions

The interaction of nepafenac with P-glycoprotein and other transporters was not assessed. However, given the ocular administration, low systemic exposure and rapid plasma clearance, inhibition of transporters is considered unlikely. The data submitted indicate that nepafenac and amfenac are unlikely to inhibit CYP450 enzymes at clinical exposures. The Cmax for nepafenac was >3500×, and amfenac was >500×, the highest concentrations used to test in vitro inhibition of CYP450s.

Toxicology

Acute toxicity

Acute toxicity of nepafenac was assessed with doses of 1000-2000 mg/kg IP and PO in ICR mice, and 100-500 mg/kg intraperitoneal (IP) and 100-1000 mg/kg oral (PO) in SD rats. Following a 14 day observation period, the maximum non-lethal dose was 2000 mg/kg PO and 1000 mg/kg IP in mice, and 100 mg/kg IP and PO in rats. The target organ in rats appeared to be the stomach. Acute toxicity by the clinical route was not examined, but given the limited ability to achieve high doses by the topical ocular route this is acceptable. Following PO and IP dosing, nepafenac has a moderate order of acute toxicity.

Repeat-dose toxicity

Studies of up to 6 months duration in SD and Fischer rats (PO) and NZW and pigmented rabbits (ocular), a 3 month study in cynomolgus monkeys (ocular), and a 9 month study in rabbits (ocular) were conducted to assess both ocular (rabbits and monkeys) and systemic toxicity. The species selected and duration of studies were adequate given the proposed short-term use (≤22 days). Ocular dosing frequency ranged from 1-4 times daily in rabbits, and was four times daily in monkeys. The conduct of the pivotal studies was consistent with the relevant guidelines.[5] While no major deficiencies were noted, the omission of recovery groups from the repeat dose studies is a limitation.

[5] European Medicines Agency, "Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*)", 18 March 2010.

Relative exposure

Both systemic and ocular exposure ratios were calculated. Due to similar pharmacological activities, exposure ratios were calculated based on additive plasma AUC for nepafenac and amfenac. Total AUC values were used as plasma protein binding data were not available for all species or for amfenac. The 6 month rabbit study (TDOC-0001960) was selected to calculate relative exposure as this study achieved higher ocular exposures compared to the 9 month study (TDOC-0004477).[6] To calculate exposure ratios for the 6 month rabbit study, AUC data were multiplied by a factor of 3, as nepafenac was administered TID, with AUC data collected after a single administration. Similarly, AUC data were multiplied by a factor of 4 for the 3 month monkey study (TDOC-0001434), as nepafenac was administered QID, with AUC data calculated after a single administration. Relative exposure was very high in rats following oral dosing, and high in rabbits following single or multiple daily dosing. It should be noted that the exposure ratios in rats and rabbits are likely to be underestimated as the first blood samples were taken after the expected Cmax. This is not considered a deficiency as it leads to a more conservative estimate of relative exposure.

Ocular exposures were calculated based on mg nepafenac applied per eye per day, as exposure to nepafenac and amfenac was shown to accumulate with multiple daily dosing in most ocular tissues. The dose was adjusted for eye volume.[7] Relative ocular exposures were moderate to high in the pivotal rabbit and monkey studies.

[6] In the 6 month study nepafenac was administered at a higher dose (1.5%), and unilaterally (2 drops OD TID; total 6 drops per eye), as opposed to bilateral dosing with a lower concentration in the 9 month study (1 drop, 1%, OU QID; giving 4 drops per eye).

[7] Short, BG. Safety Evaluation of Ocular Drug Delivery Formulations: Techniques and Practical Considerations. *Toxicologic Pathology* 36: 49-62 (2008).

Table 3: Relative exposure in repeat dose toxicity studies.

Species	Study duration & treatment details (study number)		Dose		Nepafenac + Amfenac AUC_{0-t}^ (ng·h/mL)	Exposure Ratio	
			mg/kg	mg/eye /day		Systemic#	Ocular*
Rat (SD)	6 months [PO]; (TDOC-0001935)		1	–	92	18	–
			3	–	401	78	–
			10	–	1739	339	–
Rabbit (NZW×NZR, pigmented)	1 month; 1 drop, OU, clinical formulation (TDOC-0010277)	0.3%	0.06	0.1	57	11	2.2
		0.6%	0.12	0.2	84	16	4.9
		1%	0.20	0.4	117	23	8.1
		1.5%	0.30	0.6	138	27	12
	6 months; 2 drops, TID, OD (TDOC-0001960)	0.3%	0.2	0.7	35	6.7	16
		1%	0.8	2.4	62	12	53
		1.5%	1.2	3.6	170	33	80
	9 months; 1 drop, QID, OU (TDOC-0004477)	0.1%	0.1	0.2	36	7.1	3.6
		0.3%	0.5	0.5	214	42	11
		1%	1.1	1.6	254	50	36
Monkey (Cynomolgus)	3 months; 2 drops, QID, OD (TDOC-0001434)	0.1%	0.06	0.3	34	6.6	3.3
		0.3%	0.2	1.0	103	20	10
		1%	0.6	3.2	325	63	33
Human (healthy volunteers)	4 days; 1 drop OU 0.3% nepafenac (TDOC-00012899)		*ca.* 0.005*f*	0.12	5.1	–	–

^ AUC0-t reported in animal studies, with t ≤ 4h, therefore exposure may be underestimated, but multiple daily dosing was accounted for $AUC_{0-\infty}$ reported in humans
# Animal AUC_{0-t}: human AUC based on total nepafenac and amfenac
* mg/eye adjusted for eye volume, assuming a vitreous volume of 1.5, 3.2 and 4.0 mL in rabbits, monkeys and humans, respectively
f based on 1×40 µL drop per eye per day in a 50 kg adult
Note, the drop volume was not indicated for Ilevro, so a volume of 40 µL was estimated based on the largest drop volume used in animal studies.

Major toxicities

The major toxicities for nepafenac involved the gastrointestinal tract, kidneys and erythroid cells, with some effects also observed on cornea, lens and ovaries.

Following high oral dosing (≥30 mg/kg/day), nepafenac was associated with significant gastrointestinal toxicity in pregnant rats. Toxicity was characterised by gastrointestinal lesions, perforation and erosion of the mucosa, abnormal gastrointestinal contents and abdominal adhesions. Serositis was also observed in the jejunum of female rats (5/10) that received 25 mg/kg/day (relative exposure >339, Study 131:38520:0995). These are known class effects of NSAIDs. Given the relatively low systemic exposure following topical ocular dosing they are unlikely to occur clinically with nepafenac.

Renal papillary necrosis, a known NSAID class effect, was observed in 2 of 10 female rats that received 15 mg/kg/day PO nepafenac for 3 months (relative exposure >339). Similar to gastrointestinal toxicity, this effect is unlikely to occur clinically.

Nepafenac decreased red blood cell numbers and haemoglobin following high oral doses in SD rats (≥15 mg/kg/day), which was associated with extramedullary haematopoiesis. However, adverse effects on erythroid parameters were not observed following 6 months oral administration of nepafenac to Fischer rats (≤10 mg/kg/day), which achieved relative exposures of 339× that expected clinically. Therefore, adverse effects on erythroid parameters are unlikely to occur with the proposed indication for nepafenac.

Corneal opacity was observed in one male SD rat that received 7.5 mg/kg/day PO nepafenac for 2 weeks. Corneal opacity was not observed in longer term rat studies, or with ocular administration in rats and monkeys. However, corneal opacity has been reported as an adverse effect clinically, and therefore a relationship to treatment cannot be excluded. In addition, corneal mineralisation was observed in 5 of 25 male rats that received 10 mg/kg/day PO nepafenac for 6 months (relative exposure 339). As no recovery group was included in this study it is unclear if this effect is reversible. Corneal mineralisation was not observed in rabbits or monkeys following topical ocular dosing, which achieved relatively high ocular and systemic exposures to nepafenac.

Cataracts developed in two studies of topical ocular administration. In pigmented rabbits, 1 of 4 LD males (0.3% nepafenac OU) and 1 of 4 mid dose female (1% nepafenac OU) each developed a unilateral cataract on day 6/7 of a one month study (relative ocular exposures of 2 and 8, respectively). The sponsor indicated the development of these cataracts was not treatment related as there was no dose response and the cataracts developed in one eye only and relatively early in the treatment phase. The sponsor also provided a reference indicating the background rate of juvenile cataracts to be 1.1% in the strain used (NZW×NZR). In the monkey study, bilateral cataracts developed in a LD male despite treatment only in the right eye (relative ocular exposure 3). Overall, the weight of evidence indicates these cataracts are likely to be spontaneous. Furthermore, the proposed indication is associated with cataract surgery which diminishes the potential risk. However, should nepafenac be considered for other ocular indications, further investigation of this observation may be necessary.

Increased ovarian weight and/or incidence of ovarian cysts were observed in rats the received ≥1 mg/kg/day PO nepafenac (relative exposure ≥18). There were no microscopic correlates. In addition, no clear treatment related effects were observed in ovaries following ocular administration in rabbits or monkeys. Oral dosing of nepafenac did not affect oestrus cycles in rats. COX-2 is expressed in ovaries, and therefore these effects may be treatment related. However, the low systemic exposure and short duration of treatment clinically decreases toxicological concern.

Overall, the repeat dose toxicity studies indicate that there is minimal toxicological concern for the proposed short term, topical ocular use of nepafenac.

Genotoxicity

Genotoxicity was assessed in a standard battery of assays, consisting of a bacterial mutagenesis assay, mammalian mutagenesis assay, as well as in vitro and in vivo clastogenicity assays. The studies conducted were consistent with ICH guideline S2 (R1)[8] in terms of study type, study design, concentrations and doses of nepafenac tested and route of exposure in the in vivo study.

Nepafenac did not increase mutation frequency in the bacterial reverse mutagenesis assay or mouse lymphoma assay. Nepafenac induced both structural and numerical chromosomal aberrations in vitro in the presence and absence of metabolic activation. In vivo, nepafenac did not induce chromosomal aberrations in mice, even at very high doses (5000 mg/kg PO) and up to 72 h after dosing. The weight of evidence from the studies conducted indicates that nepafenac is not genotoxic.

[8] International Conference on Harmonisation, "Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (S2[R1])", 9 November 2011.

Carcinogenicity

Carcinogenicity studies were not submitted which is acceptable given the short-term indication for nepafenac (ICH guideline S1A).[9]

Reproductive toxicity

The reproductive toxicity studies conducted were consistent with ICH guideline S5 (R2),[10] and all studies used oral dosing of nepafenac at the appropriate times to assess reproductive toxicity. The studies conducted included one fertility study in SD rats, pilot and pivotal embryofoetal development studies in SD rats and NZW rabbits, and a pre/postnatal study in SD rats. Toxicokinetic data were obtained only for the pivotal embryofoetal development studies in rats and rabbits, and very high exposure ratios were achieved in both species (Table 4). In the fertility, pre/postnatal, and pilot embryofoetal development studies, estimated exposure was also high (see below). In the rat fertility study, the high dose level (30 mg/kg/day) was reduced to 15 mg/kg/day due to excessive toxicity and/or mortality. Similarly, a 15 mg/kg/day group was added to the pre/postnatal rat studies due to excessive maternal toxicity and/or mortality in rats receiving 30 mg/kg/day.

Table 4: Relative exposure in reproductive toxicity studies.

Species	Study	Dose (mg/kg/day)	Nepafenac + Amfenac AUC_{0-t} (ng·h/mL)	Exposure ratio#
Rat (SD)	Embryofetal development (156:30:0801) (TK: TDOC-0001901)	3	862	168
		10	4397	857
		30	18560	3618
Rabbit (NZW)	Embryofetal development (157:30:0801) (TK: TDOC-0002069)	3	153	30
		10	691	135
		30	5032	981
Human (healthy volunteers)	4 days; 1 drop OU 0.3% nepafenac (TDOC-00012899)	*ca.* 0.005^	5.13	–

Placental transfer of radioactivity was demonstrated following oral dosing of 3 mg/kg 14C nepafenac rats. Radioactivity was detected in foetal tissues as well as blood and amniotic fluid, with levels lower than maternal plasma levels. Further studies were not conducted to characterise which entities crossed the placental barrier (nepafenac, amfenac and/or other metabolites). Excretion of radioactivity into milk was also demonstrated in lactating rats following oral dosing of 14C nepafenac. The concentration in milk was similar to that observed in the blood of lactating rats, indicating that nepafenac and/or its metabolites did not preferentially distribute to the milk.

The effects of nepafenac on fertility were studied in SD rats (3-15 mg/kg/day PO). At the highest dose, body weight gain was reduced in males and females. Sperm motility and concentration were decreased without effect on reproductive indices in males that received 15 mg/kg/day (estimated[11] relative exposure >300). In females, nepafenac had no adverse effect on fertility (oestrous cycle, copulation, fertility index). However, the number of viable foetuses per dam was decreased associated with increased early

[9] International Conference on Harmonisation, "Guideline on the need for carcinogenicity studies of pharmaceuticals (S1A)", 29 November 1995.
[10] International Conference on Harmonisation, "ICH Topic S 5 (R2): Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility", March 1994.
[11] An estimate based on the exposure ratio at 10 mg/kg/day PO in Study TDOC-0001935 (Table 3).

resorptions in dams that received ≥10 mg/kg/day (estimated relative exposure ≥800), so the NOAEL was 3 mg/kg/day (estimated relative exposure 170).[12]

Nepafenac (3-30 mg/kg/day PO) was administered to pregnant SD rats and NZW rabbits during the period of organogenesis to assess effects on embryofoetal development. The high dose was associated with significant maternal toxicity in rats, with mortality in 5 of 25 dams. Body weight gain was also decreased in dams that received ≥10 mg/kg/day (relative exposure ≥857). One high dose dam had no viable foetuses, but there were no other signals of embryofoetal lethality. Foetal body weight was decreased by 6% in the offspring of dams that received 30 mg/kg/day (likely secondary to maternal toxicity). No treatment-related malformations were observed, but there was a treatment-related increase in skeletal variations in offspring from the high dose group (unossified sternebrae, 7th cervical rib). In rabbits, body weight and food intake tended to be decreased in the low dose and high dose group, without a clear treatment related effect. A single litter was spontaneously aborted in both the mid and high dose groups (relative exposure ≥135), with a premature delivery also occurring in the high dose group. The incidence of total and skeletal malformations was significantly increased in the high dose group. Visceral malformations included major heart and blood vessel malformations which have previously been reported for NSAID. Skeletal malformations included anomalies in the thoracic vertebrae, ribs and costal cartilage. The NOEL for maternal toxicity was 3 mg/kg/day in rats and rabbits (relative exposure 168× and 30×, respectively). The NOEL for embryofoetal developmental toxicity was 10 mg/kg/day in rats and rabbits treated during organogenesis (relative exposure 857× and 135×, respectively).

Maternal toxicity and mortality occurred in SD rats following oral dosing of nepafenac (3–30 mg/kg/day) from the beginning of organogenesis to the end of lactation. Maternal toxicity was associated with reduced body weight gain and food intake and adverse clinical signs including decreased activity, paleness, cool to touch and abnormal excreta (≥10 mg/kg/day, relative exposure 857×). At the highest dose significant mortality occurred prior to delivery (10 of 25 rats that received 30 mg/kg/day). At parturition, there was a dose dependent increase in dam mortality with retained foetuses observed at necroscopy (≥3 mg/kg/day, relative exposure ≥168). On lactation day 0, the number of dead pups was increased and liver litter size decreased in dams that received ≥15 mg/kg/day, with pup survival also lower on lactation days 1 and 4. Excessive toxicity in dams receiving 30 mg/kg/day led to euthanasia of surviving pups in this group. F1 pup mortality was associated with increased incidence of gasping and slow respiration, pups being cool to touch and increased incidence of cannibalisation. Initially, F1 pup weight was reduced by ≥10% in offspring of dams that received 10 or 30 mg/kg/day nepafenac. Body weights were similar between groups at weaning, but after that were generally ca. 5% lower in offspring of dams that received ≥15 mg/kg/day compared to controls. There were no significant effects on F1 pup development, behaviour, survival or reproductive performance. Due to maternal mortality at parturition a NOAEL could not be established for maternal toxicity. The observations are consistent with known class effects of NSAIDs. The NOEL for developmental toxicity in F1 offspring was 3 mg/kg/day.

Thus, very high relative exposures were associated with malformations in rabbits, but not rats. In rats, prolongation of treatment from the end of organogenesis to weaning elicited greater F0 and F1 toxicity, compared to treatment confined to the period of organogenesis.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[13] This is appropriate based on the nonclinical findings, and is consistent with other NSAIDs.

[12] Estimates based on the exposure ratios at 3 and 10 mg/kg/day PO in Study 156:30:0801 (Table 4).

Local tolerance

Ocular tolerance was adequately assessed in the repeat dose toxicity studies, consistent with EU guideline.[14] Daily topical ocular dosing for 1 month with up to 1.5% nepafenac in the clinical formulation was not associated with ocular irritation in pigmented rabbits. Similarly, topical ocular dosing did not cause adverse ocular effects in pigmented rabbits (≤1.5%, TID for 6 months) or cynomolgus monkeys (≤1%, QID for 3 months).

Antigenicity

The skin sensitisation potential of nepafenac was assessed using the guinea pig maximisation study. The study was conducted by a validated method and tested concentrations that exceeded the clinical formulation of nepafenac. Nepafenac was not a skin sensitiser under the conditions tested.

Phototoxicity

The phototoxicity of nepafenac and amfenac were assessed in a validated in vitro assay (3T3 Neutral Red uptake). Nepafenac and amfenac were not cytotoxic in the presence or absence of UV light. No further testing for phototoxicity was performed which is consistent with ICH guideline S10.[15]

Impurities

One degradant impurity in the drug product was toxicologically qualified.

Paediatric use

Nepafenac is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Safety Specification of the Risk Management Plan (RMP)

Results and conclusions drawn from the nonclinical program for nepafenac detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator. However, the exposure ratios are inaccurate for Ilevro as they appear to have been based on human dosing with 0.1% nepafenac. While the safety margins are lower based on nepafenac alone, the exposure ratios should be calculated for the sum of nepafenac and its active metabolite, amfenac. Therefore, the safety margins in pregnant rats and rabbits should be ≥155 and ≥135, respectively, based on Cmax and AUC values derived from the sum of nepafenac and amfenac, and human values determined after once daily topical ocular dosing with 0.3% nepafenac.

[13] Pregnancy Category C: "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details."
[14] European Medicines Agency, "Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)", 1 March 2001.
[15] International Conference on Harmonisation, "Photosafety evaluation of pharmaceuticals (S10)", 13 November 2013.

Nonclinical summary and conclusions

Summary

- The dossier adequately addressed appropriate ICH guidelines. Pivotal toxicity studies were GLP compliant, but safety pharmacology studies of nepafenac were not.
- Nepafenac and its pharmacologically active metabolite, amfenac, both inhibited COX-1 and to a lesser extent COX-2. When compared directly, nepafenac was a more potent COX inhibitor than amfenac. Nepafenac was converted to amfenac in anterior and posterior ocular tissues. Topical ocular administration rapidly inhibited ex vivo prostaglandin synthesis in the ICB and retina/choroid tissues, with PGE2 synthesis in ICB inhibited by ≥57% for up to 24 h. In vivo, topical ocular nepafenac inhibited trauma induced PGE2 accumulation in aqueous humour and breakdown of the blood-aqueous barrier.
- Secondary pharmacodynamics studies showed that nepafenac inhibited choroid and preretinal revascularisation in rodents and rabbits, and rodent models of oxygen induced retinopathy. Nepafenac also attenuated diabetes induced retinopathy but not retinal permeability. Nepafenac did not interact with the 21 receptors and binding sites tested.
- Safety pharmacology studies did not identify any specific risks of nepafenac, but studies were not GLP compliant. In vitro cardiovascular safety studies were not conducted with nepafenac. However, GLP compliant in vitro and in vivo studies of amfenac did not identify any adverse cardiovascular effects at concentrations up to 88× (in vitro) and >10,000× (in vivo) the clinical Cmax for amfenac.
- Nepafenac has moderate ocular bioavailability, with rapid absorption and short systemic half life in humans, rabbits and monkeys. The ocular half-life of nepafenac and amfenac was biphasic, with a prolonged terminal elimination. Nepafenac was rapidly metabolised to amfenac, the major, pharmacologically active, metabolite in ocular tissues. Systemic exposure (as AUC) to amfenac was greater than nepafenac in humans and animals. The similarity of other minor metabolites (<10%) between humans and laboratory animals was not fully determined as not all metabolites were identified. Nepafenac and amfenac did not induce or inhibit CYP450 enzymes at concentrations or exposures (Cmax) >100× that expected clinically.
- Nepafenac had a moderate order of acute toxicity via the PO and IP routes, but high systemic exposure is unlikely with the proposed clinical formulation.
- Repeat dose studies were conducted in rats (PO, ≤6 months), rabbits (ocular, ≤6 months) and monkeys (ocular, 3 months). These studies achieved high systemic and ocular relative exposures. NSAID class effects were observed at very high relative exposures, including gastrointestinal toxicity, renal papillary necrosis and mild anaemia (>339× based on the sum of nepafenac and amfenac AUC). Increased ovarian weight and/or incidence of ovarian cysts occurred in rats (≥1 mg/kg/day PO), but did not occur in other species with ocular nepafenac administration. Corneal opacity and or mineralisation were observed in male rats that received ≥7.5 mg/kg/day PO for ≥2 weeks (relative exposure >78). Isolated cataracts occurred in two rabbits and one monkey, but did not appear to be treatment related.
- Nepafenac was not mutagenic in bacterial or mammalian cells in vitro. Nepafenac increased the incidence of numerical and structural chromosomal aberrations in vitro, but was not clastogenic in vivo. The weight of evidence indicates nepafenac is not genotoxic. Carcinogenicity was not assessed which is acceptable given the proposed dosing duration.

- Nepafenac crosses the placenta and is excreted into the milk of lactating rats. At high doses (10 mg/kg/day PO, relative exposure >300), nepafenac reduced sperm motility in male rats and increased early resorptions in female rats, but fertility was unaffected. Reduced foetal weight and increased skeletal variations occurred in association with maternal toxicity in rats that received nepafenac during organogenesis (30 mg/kg/day PO, relative exposure ~3600), without evidence of malformations. In rabbits, high dose oral nepafenac during organogenesis increased the rate of visceral and skeletal malformations (30 mg/kg/day, relative exposure ~980); the no effect dose was 10 mg/kg/day (relative exposure 135). A pre/postnatal study in rats demonstrated maternal mortality at or around parturition in dams that received ≥3 mg/kg/day PO (relative exposure ≥170). Live births and pup weight and survival were decreased in offspring of dams that received ≥10 mg/kg/day. Based on mortality, a maternal NOAEL could not be established. Overall, the NOAEL for embryofetal developmental toxicity was 10 mg/kg/day in rats and rabbits (respective relative exposures 850 and 135), and 3 mg/kg/day for developmental toxicity in F1 offspring (relative exposure 170).
- Ocular tolerance was assessed in repeat dose toxicity studies, with no ocular irritation observed with nepafenac suspensions of ≤1.5% dosed up to four times daily. The clinical formulation was also assessed in pigmented rabbits with no adverse effects.
- Nepafenac was not phototoxic in a validated assay (3T3 neutral red uptake).
- Nepafenac was not a skin sensitiser in the guinea pig maximisation assay.
- One degradant impurity in the drug product was adequately qualified.

Conclusions and recommendation

- The primary pharmacology studies support the proposed indication and route of administration.
- The safety pharmacology (non GLP compliant) studies did not identify any specific hazards. The incomplete cardiovascular safety assessment of nepafenac is offset by low systemic exposure, history of clinical use overseas and negative results in GLP compliant studies of amfenac.
- The repeat dose studies identified NSAID class effects, but these are unlikely to occur clinically at the low systemic exposure. At very high relative exposures adverse corneal effects were observed in rats (opacity and mineralisation).
- Nepafenac has a low genotoxic potential, and carcinogenicity was not investigated due to short duration of use.
- Consistent with known NSAID effects, nepafenac is maternally toxic and teratogenic in animal studies, but only at very high relative exposures.
- Nepafenac did not cause ocular or skin irritation, or skin sensitisation.
- There are no nonclinical objections to registration of Ilevro as proposed.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The rationale for using a NSAID, pre and post cataract surgery, was to minimise pain and inflammation that resulted from surgical trauma.

Guidance

A pre submission meeting between officers of the TGA and representatives of the sponsor did not precede the application. However, a pre submission planning letter dated 15 October 2014 requested further nonclinical data to be added to the submission dossier.

There is no TGA adopted guideline for cataract treatment.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 Phase I study that provided pharmacokinetic (PK) data (C-09-053) and 3 additional Phase I PK studies (C-05-08; C-04-27; C-05-19).[16]
- 1 Phase III pivotal efficacy/study (C-09-055).
- 1 Phase II pivotal efficacy/safety study (C-11-003).
- 1 Periodic safety update report (PSUR) for nepafenac 0.1% eye drops (covering period 01/12/10 to 30/11/11).
- 1 Integrated summary of safety (ISS).

Evaluator's comments: The clinical dossier did not document a full development program of clinical pharmacology, efficacy and safety studies. The data package was deficient in respect of clinical pharmacology. No human pharmacodynamic (PD) studies were provided in this application. Refer to the relevant findings from the Non-clinical Evaluator's report.

The data package was intended for regulatory agencies that already marketed nepafenac 0.1% eye drops. In the proposed Australian PI the annotations that related to 'source documents' were cross referenced to particular sections in the EU SmPC rather than the actual clinical data from which the information were derived. Many hyperlinks did not work, especially for links between modules.

Fenazox is not available in Australia and the clinical data provided in this submission for Fenazox were limited. However, this evaluation report will refer to Fenazox in the pharmacology and clinical safety sections of this report.

The New Zealand Data Sheet for Ilevro was provided however, an application for Ilevro was not submitted to NZ at the time of this application.

Paediatric data

The submission did not include paediatric data. Specific studies in the paediatric population were considered unnecessary as cataract surgery is uncommon in children. When anterior surgery is required, steroidal preparations are the mainstay of treatment, as children are more sensitive to post operative inflammation.

[16] Three additional clinical study reports and four references were provided upon request, which included Fenazox prescribing information.

Good clinical practice

The submitted studies were stated to have been conducted in compliance with Good Clinical Practice (GCP), including the archival of essential documents. All studies were conducted according to appropriate ethical standards.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the PK studies. No PK study had deficiencies that excluded their results from consideration.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	C-09-053 C-05-08 (Japanese)	* *
	- Multi-dose	C-09-053 C-05-08 (Japanese)	* *
	Excretion/metabolism	C-04-27	*
	Gender	C-05-08	
PK in target population	General PK - Single dose	C-05-19	*

* Indicates the primary study aim

Evaluator's conclusions on pharmacokinetics

The data package was limited to four human PK studies (three obtained on further request) that examined single dose and multiple dose PK in healthy adult volunteers with the nepafenac 0.3% ophthalmic suspension, single dose and multiple dose PK in the target population using nepafenac 0.1% eye drops (with ketorolac 0.4% as active control) and a radiolabelled study that demonstrated the metabolism and excretion of a single oral dose of 14C nepafenac.

No clinical studies on bioavailability or bioequivalence were provided in this submission on the basis of limited systemic exposure of nepafenac 0.3% eye drops and the registration of a single product. This is reasonable.

Nepafenac and its active metabolite, amfenac, demonstrated rapid absorption with Tmax in one hour or less, in both healthy subjects and the target population. Hence, administration of nepafenac 0.3% topically within 30 to 120 minutes before cataract surgery, as proposed by the sponsor, should coincide with the maximum concentrations of nepafenac and amfenac achieved within intraocular tissue. This is desirable.

Once daily dosing of nepafenac 0.3% eye drops is supported by the amfenac half life > 6 hours and the three fold increase in Cmax for amfenac in the nepafenac 0.3% formulation compared with the nepafenac 0.1% formulation.

Nepafenac and amfenac demonstrated low systemic exposure following 4 days of once daily bilateral topical ocular dosing of nepafenac 0.3% eye drops in both healthy adult US subjects (Study C-09-053) and healthy adult Japanese male and female subjects (Study C-05-08). Furthermore, nepafenac and amfenac did not appear to accumulate after 4 days of multiple dosing (that is, at steady state).

Similar aqueous humour exposure was noted between amfenac (from nepafenac 0.1% eye drops) and ketorolac 0.4%. Given the differences in strength, particle size and formulation between the nepafenac 0.1% used in Study C-05-19 and the proposed nepafenac 0.3% preparation it is difficult to extrapolate these results to the higher strength formulation. Greater exposure with nepafenac 0.3% would be expected based on other PK results.

There appeared to be minimal uptake and retention of radioactivity by red blood cells or haemoglobin. Urinary excretion accounted for 85.5% of radioactivity from a 10 mg dose of nepafenac oral suspension and 6.2% of radioactivity from a 10 mg dose was excreted in faeces. Nepafenac was extensively metabolised with eight glucuronide metabolites (other than unconjugated amfenac) identified in plasma. It is unclear whether any metabolite other than amfenac had pharmacological activity.

PK drug interactions are unlikely to occur or they are likely to be clinically insignificant based on lack of effect on hepatic cytochrome P450 enzymes, and the low systemic exposure of nepafenac and amfenac.

On the basis of limited systemic exposure of topical nepafenac 0.3% eye drops, no dose adjustments would be expected for subjects with impaired hepatic or renal function, or by gender or age (as cataract surgery is primarily targeted in an elderly population, which formed the majority of subjects studied in the nepafenac clinical development program). These assumptions are reasonable.

Generally, PK data from oral Fenazox were consistent with PK from ophthalmic nepafenac 0.3%.

Pharmacodynamics

Nonclinical PD data indicated nepafenac is effective in suppressing PGE2 synthesis in rabbits for over 30 hours following a single dose at a concentration of 3 mg/mL, in both the anterior and posterior chambers of the eye.

Given the low systemic exposure to nepafenac in humans, the sponsor did not conduct a specific QT study or PD interaction studies for the nepafenac 0.3% preparation, or the commercially available 0.1% preparation (Nevanac). This is reasonable. Furthermore, to date, no drug interactions have been reported with the nepafenac 0.1% and 0.3% preparations.

Dosage selection for the pivotal studies

From Study C-11-003 Clinical Safety Report:

The drug concentration (0.3%) for this study was considered safe based upon the results of nonclinical studies and previous clinical trials. During the clinical development of nepafenac, patients were exposed to various concentration formulations ranging from 0.003% to 0.3% for up to 6 months. Adverse reactions in patients exposed to 0.3% nepafenac concentrations during previous clinical trials were mild in intensity, and resolved with or without treatment, except for 1 event (cataract) which was continuing without treatment when the patient exited from the study.

In a pharmacokinetic animal model, nepafenac 0.3% dosed once daily resulted in steady state drug levels (nepafenac and amfenac) in the ICB that were significantly higher than those for nepafenac 0.1% when dosed once daily or 3 times daily. The once daily formulation had similar cumulative exposure levels over a 24 hour period to those observed with nepafenac 0.1% dosed 3 times daily. The dosing regimen of once daily rather than 3 times daily is expected to be more convenient for the patient and result in improved compliance for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery.

Efficacy

Studies providing efficacy data

The pivotal efficacy studies, C-11-003 and C-09-055, are considered together in this section because their study design, entry criteria, treatments, randomisation and blinding methods, efficacy variables and statistical methods were similar. Any notable differences are discussed in the relevant sub-section.

The sponsor provided multiple comparisons in the efficacy studies of the nepafenac 0.1% eye preparation versus nepafenac vehicle 0.1%. Given nepafenac 0.1% is not proposed to be marketed in Australia at the time of the application, the latter results are considered supportive of the nepafenac 0.3% application and will not be discussed in great detail in this CER. However, in Study C-09-055, a non inferiority comparison of nepafenac 0.3% versus nepafenac 0.1% was a co-primary endpoint.

Evaluator's conclusions on efficacy

The pivotal efficacy studies (C-11-003 and C-09-055) were generally well designed, controlled (active and vehicle) trials using subjects with comparable baseline characteristics , in a population who would be expected to benefit from treatment from cataract surgery, that is, an elderly, predominantly female group. However, while the sponsor provided primary efficacy analyses for postoperative inflammation, postoperative pain was only assessed as a secondary efficacy endpoint in Study C-09-055 and supportive efficacy endpoints in Studies C-09-055 and C-11-003, that is, no primary efficacy analysis of postoperative pain was undertaken. This is important as the sponsor's application is for an indication in both postoperative inflammation and postoperative pain associated with cataract surgery. Further information on postoperative pain will be requested.

The cure rates and rate differences in the primary efficacy analysis for nepafenac 0.3% versus nepafenac vehicle 0.3% were consistent between the efficacy trials and NNT of 3 patients in each trial is clinically significant. Further, in Acular (ketorolac) clinical trials in post operative inflammation, approximately 39% of ketorolac patients achieved a zero score for anterior cells and flare after 2 weeks of treatment compared with 12% of placebo patients.[17] The treatment difference of 27% equates to a number needed to treat (NNT) of

[17] Acular Australian PI.

4 (1/0.27). Hence, the nepafenac 0.3% results are similar to the results achieved with the Australian approved product, Acular, for the treatment of post operative inflammation. There are no comparative endpoints for pain in the Acular PI.

The subgroup analyses of the primary efficacy endpoint, secondary efficacy results, supportive and exploratory results, across all efficacy trials, were consistent with the primary efficacy results. In particular, statistical separation between nepafenac 0.3% and nepafenac vehicle 0.3% occurred early in the studies (often from the Day 1 post operatively) in inflammatory scores (mean aqueous cells and flare). These scores improved in the nepafenac 0.3% groups throughout the 14 day study period. Hence, nepafenac 0.3% provided a reduction in early postoperative inflammation compared with nepafenac vehicle 0.3%.

Treatment failures were in the order of 10 fold less in the nepafenac 0.3% treatment groups compared with the nepafenac vehicle 0.3% groups. These differences were noted from the Day 1 post operative visit, with most of the difference between active treatment with nepafenac and its vehicle treatment achieved within the first 7 days.

In the primary efficacy analysis in Study C-09-055, nepafenac 0.3% dosed once daily was non inferior to nepafenac 0.1% dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

Generally, the comparative analyses of nepafenac 0.1% versus nepafenac vehicle 0.1% provided similar results, of similar magnitude, to the nepafenac 0.3% versus nepafenac vehicle 0.3% analyses performed across the efficacy trials. The nepafenac 0.1% results therefore provided supportive efficacy data for the nepafenac 0.3% strength preparation proposed in this submission.

Safety

Studies providing safety data

Pivotal studies that assessed safety as a primary outcome

Studies C-11-003 and C-09-055 were pivotal studies that assessed safety as a primary outcome. These studies are described. In this section of the clinical evaluation report, the pooled results (from the ISS) were used for the pivotal studies. Each individual clinical safety report (CSR) was reviewed and the results compared with the ISS results. Any notable differences are discussed in the relevant sub-section.

Other studies evaluable for safety: Clinical pharmacology studies

In addition, safety assessments were measured in healthy subjects exposed to nepafenac 0.3% eye drops in the Phase I PK trial (C-09-053). These measurements, which served as supportive safety information included extent of exposure to study drug, adverse events (AEs), and other safety related parameters such as best corrected visual acuity (BCVA), ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens), intraocular pressure (IOP) and dilated fundus parameters (vitreous, retina/macula/choroid, and optic nerve) and clinical laboratory examinations (haematology, blood chemistry, and urinalysis).

Safety data on the 7 Japanese subjects who received nepafenac 0.3% treatment in Study C-05-08, an additional clinical pharmacology provided during the first round clinical evaluation are not included in the pooled data, as they were not included in the integrated safety set.

Studies C-05-19 and C-04-27, two additional clinical pharmacology studies the sponsor provided, did not include subjects exposed to nepafenac 0.3% treatment.

Patient exposure

N/A

Safety issues with the potential for major regulatory impact

N/A

Post marketing data

As provided by the sponsor:

> *Nepafenac eye drops, suspensions are currently marketed as Nepafenac 1 mg/mL, eye drops, suspension and Nepafenac 3 mg/mL, eye drops suspension. Data from post marketing experience involving each of these products will be described below.*
>
> *The first Alcon product containing nepafenac for ocular use (Nevanac, Nepafenac 1 mg/mL, eye drops, suspension was approved in the US in August 2005. In December 2007, this product was first approved by European Medicines Agency (EMA). Currently, Alcon has registered nepafenac containing products for ocular use (ophthalmic nepafenac at concentrations of 1 mg/mL and 3 mg/mL) in over 90 countries worldwide.*
>
> *From product launch in 2005 up to 30 April 2014, 30,237,833 units of Nevanac have been distributed worldwide by Alcon. From product launch in 2012 up to 30 April 2014, 522,473 units of Nepafenac 3 mg/mL eye drops suspension have been distributed worldwide by Alcon.*

AEs possibly associated with the ocular use of nepafenac are varied, generally non-serious and mostly related to local ocular disorders. As of 30 April 2014, there were 1710 post-marketing AEs for nepafenac 0.1% ophthalmic preparation, of which 919 (53.7%) were categorised under 'eye disorders'. In contrast, for Ilevro, as of 30 April 2014, there were 68 (63.0%) AEs classified under 'eye disorders' from a total of 108 spontaneous AE reports. There have been no regulatory actions related to safety since the marketing of Nevanac (nepafenac 0.1% eye drops suspension) and nepafenac 0.3% eye drops suspension.

> *Evaluator's comment: While no new safety signal compared with the nepafenac 0.1% eye drops has been noted to date, the exposure to nepafenac 0.3% is limited at the time of this review. Furthermore, the PSUR submitted with this application included data for the period up to the end of November 2011. This PSUR did not include data for nepafenac 0.1% in the treatment of diabetic patients.*

Evaluator's conclusions on safety

Most AEs observed in the post cataract inflammation studies (C-09-055 and C-11-003) for nepafenac 0.3% eye drops were local/ocular. AEs tended to occur in the first week after cataract surgery, with mild or moderate intensity. Few subjects experienced serious adverse events (SAEs) (0.9% who received nepafenac 0.3% across trials), although one elderly subject in Study C-09-055 withdrew from the study due to a treatment related hypersensitivity reaction (facial allergic reaction). No deaths were reported for nepafenac eye drops throughout the clinical development program.

Headache incidence was greater than 1% in all treatment groups, with an apparent dose-response trend. Headache was also an observed AE for Acular and Voltaren Ophtha.

There appeared to be a dose response trend in elevated intraocular pressure (IOP). While the investigators did not consider a single case of raised IOP as treatment related to nepafenac (15 for nepafenac 0.3% and 7 for nepafenac 0.1%), but rather an effect of cataract surgery, the relative rise in IOP was proportionally greater in both active

treatments than their corresponding vehicles. This effect may not be clinically meaningful in the populations studied, especially given the rapid reduction towards pre baseline IOP pressures by Day 3 post operatively, but a contributory effect of nepafenac to IOP elevation cannot be ruled out. Raised IOP is indicated as an AE for Acular and Voltaren Ophtha.

No safety issues were identified for nepafenac 0.3% eye drops based upon analysis of AEs by intrinsic factors (age, gender, race, iris colour, concomitant diseases and concomitant medications). No analyses were undertaken for extrinsic factors.

No safety issues were identified for nepafenac 0.3% eye drops based upon an analysis of change from baseline in ocular and systemic parameters, which included BCVA, ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, corneal oedema, bulbar conjunctival injection, and chemosis), dilated fundus parameters (vitreous, retina/macula/choroid, and optic nerve) and clinical laboratory evaluations (haematology, blood chemistry and urinalysis).

The safety profile of nepafenac 0.3% eye drops dosed once daily up to 16 days for the treatment of post cataract surgical pain and inflammation was generally comparable with the safety profile previously established for nepafenac 0.1% eye drops suspension. The major differences are in the higher incidence of headache and IOP with the 0.3% eye drops and a higher incidence of hypersensitivity reactions with the 0.3% eye drops compared with nepafenac 0.1% eye drops (common versus rare, respectively).

Furthermore, the risks of AEs due to accidental (or intentional) ingestion of the entire contents of a 4 mL bottle (3 mL fill size) of nepafenac 0.3% eye drops suspension have not been quantified. There is an approximate doubling of the nepafenac content in the 0.3% eye drop preparation compared with the commercially available 0.1% preparation, that is, 9 mg versus 5 mg, respectively. If a 20 kg child ingested 3 mL of nepafenac 0.3% eye drops suspension, this would equate to a dose of 0.45 mg/kg, that is, up to 45% of the recommended adult dose (200 mg per day, Fenazox). This is not an insignificant amount. For example, the Voltaren Ophtha PI states 3% of the maximum adult dose is available after ingestion, that is, 15 times less exposure than for Ilevro. Hence, toxicity following accidental or intentional oral overdose may become an issue, especially in very young children or in elderly patients. The latter may have co-morbidities such as active peptic ulcer disease, which places them at greater risk of adverse health outcomes.

First round benefit-risk assessment

First round assessment of benefits

The benefits of nepafenac 0.3% eye drops in the proposed usage are:

- The cure rates and rate differences in the primary efficacy analysis for nepafenac 0.3% vs. nepafenac vehicle 0.3% were consistent between the efficacy trials and NNT of 3 patients in each trial is clinically significant. Hence, nepafenac 0.3% provided a reduction in early postoperative inflammation compared with nepafenac vehicle 0.3%;
- The subgroup analyses of the primary efficacy endpoint, secondary efficacy results, supportive and exploratory results, across all efficacy trials, were consistent with the primary efficacy results. In particular, statistical separation between nepafenac 0.3% and nepafenac vehicle 0.3% occurred early in the studies (often from the Day 1 post operative visit) in pain scores, as well as inflammatory scores (mean aqueous cells and flare);
- Treatment failures were approximately 10 fold less in the nepafenac 0.3% treatment groups compared with the nepafenac vehicle 0.3% groups. These differences were

noted from the Day 1 post operative visit, with most of the difference between active treatment with nepafenac and its vehicle treatment achieved within the first 7 days;

- Low potential for drug-drug interactions based on low systemic exposure;
- No dosage adjustment required based on age, weight, race, renal or hepatic function (based on low systemic exposure);
- The nepafenac 0.3% results were similar in magnitude to the results achieved with the Australian approved product, Acular, for treatment of postoperative inflammation following cataract surgery;
- No deaths or treatment related SAE were observed in the pivotal efficacy and safety studies;
- In the primary efficacy analysis in Study C-09-055, nepafenac 0.3% dosed once daily was non-inferior to nepafenac 0.1% dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction;
- Generally, the comparative analyses of nepafenac 0.1% versus nepafenac vehicle 0.1% provided similar results, of similar magnitude, to the nepafenac 0.3% vs. nepafenac vehicle 0.3% analyses performed across the efficacy trials. The nepafenac 0.1% results therefore provide supportive efficacy data for the nepafenac 0.3% strength preparation proposed in this submission;
- Ilevro once daily dosing provides a simpler dosage regimen than Voltaren Ophtha and Acular (patient compliance and convenience, especially if multiple eye preparations used), as well as providing an alternative to ocular corticosteroid treatments;
- Most AEs were local, non serious, mild or moderate, and transient in nature (principally occurring in the first week post operatively);
- Generally, the safety profile of nepafenac 0.3% was similar to nepafenac vehicle 0.3% (as well as nepafenac 0.1%), and consistent with other products in the class of topical NSAIDs.

Areas of uncertainty:

- The efficacy of postoperative pain following cataract surgery has not been fully determined at the time of this report;
- The generalizability of the study results to a non Caucasian population is unclear since more than 80% of study participants across the trials were Caucasian in origin, although ethnicity is not expected to impact the results significantly;
- Since both ocular prostaglandin analogues and ocular corticosteroids were excluded from clinical trials (on the basis of potential for drug-drug interactions), any effect on Ilevro efficacy is unknown.

First round assessment of risks

The risks of nepafenac in the proposed usage are:

- A dose response relationship for headache may represent a safety signal;
- A dose response relationship for elevated IOP may represent a safety signal;
- Higher rate of hypersensitivity compared with nepafenac 0.1% may represent a new (dose response) safety signal.

Class effects of topical ophthalmic NSAIDs:

- Corneal AEs (which include keratitis, epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation). These may become sight threatening in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (for example, dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time;
- Ocular bleeding, including hyphaemas, in conjunction with ocular surgery (increased bleeding time due to interference with thrombocyte aggregation);
- Slowed or delayed healing (especially with concomitant corticosteroids);
- Masking of an acute ocular infection;
- As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or operate machinery;
- Cross-sensitivity to other NSAIDs, including aspirin, and hence potential to precipitate attacks of asthma, urticaria or acute rhinitis in susceptible individuals.

Potential safety risks:

- The safety of nepafenac 0.3% eye drops has not been established in macular oedema in subjects with proliferative diabetic retinopathy (with Nevanac use in the EU for this indication, dosage duration was up to 60 days or greater and higher AE incidence rates were noted, particularly for ocular events, for example, punctate keratitis 3%);
- Concomitant administration with topical ocular steroids (potential interaction, for example, delayed corneal healing and may act synergistically with NSAIDs in the development of ulcerative keratolysis);
- Concomitant administration with topical ocular prostaglandin analogues (for example, increase in IOP);
- The safety of nepafenac 0.3% eye drops has not been established in overdose (especially ingestion);
- Some systemic NSAIDs (for example, rofecoxib) have been found to increase the risk for serious arterial thrombotic events, including heart attack, stroke and blood clots;
- Pregnancy or nursing women;
- Use of guar as an excipient in the nepafenac 0.3% formulation (not present in the nepafenac 0.1% formulation). While AEs with guar are expected to be low, there is insufficient data at the time of this application to determine whether guar poses a safety risk;
- Use in concurrent ocular diseases, for example, dry eye, diabetic retinopathy;
- The safety of preserved nepafenac 0.3% eye drops has not been established in prolonged use. This may increase the probability of:
  - contaminated product applied to the eye(s);
  - local irritation and potential to cause punctate keratopathy and/or toxic ulcerative keratopathy from the preservative, benzalkonium chloride;
  - Repeated doses of preserved eye drops can have a cumulative effect, and the prolonged contact with the epithelium may cause chronic irritation and fibrotic changes of the conjunctiva and Tenon's capsule.

First round assessment of benefit-risk balance

Notwithstanding the deficiencies in the documentation provided in support of registration of Ilevro, much of the Nevanac information is directly relevant and, together, have provided a provisional favourable benefit-risk balance of nepafenac 0.3% eye drops, in subjects **without** diabetic retinopathy, for postoperative inflammation. The efficacy of Ilevro in post operative inflammation was similar to that observed in Acular, an Australian registered product for the proposed indication. Furthermore, the safety profile of Ilevro was generally consistent with both Acular and Voltaren Ophtha (except for omission of increased incidences of elevated IOP and headache in the Ilevro PI). The benefits of nepafenac 0.3% eye drops appear to outweigh the risks in the treatment of ocular inflammation following cataract surgery.

The sponsor has not provided sufficient data at the time of this first round report for a recommendation to approve Ilevro in postoperative pain following cataract surgery.

First round recommendation regarding authorisation

This evaluator recommends nepafenac 0.3% eye drops suspension (Ilevro) be approved for the prevention and treatment of postoperative inflammation associated with cataract surgery. However, pending further clinical data, the indication should be restricted to subjects who do not suffer from diabetes mellitus, as treatment duration may be up to four fold longer and corneal AEs are expected to be higher than for subjects who do not have diabetes mellitus. Further, until further data is provided a recommendation for Ilevro to be indicated in the prevention and treatment of postoperative pain associated with cataract surgery should be withheld.

Clinical questions

Pharmacology

Question 1

- Do any of the metabolites of nepafenac (other than amfenac) identified in Study C-04-27 have pharmacological activity? If yes, please indicate which metabolites are active and their relative activity compared with amfenac.

Question 2

- Did the sponsor undertake any pharmacokinetic studies on any of the metabolites of nepafenac (other than amfenac) identified in Study C-04-27? If so, please provide further information, particularly on Cmax, Tmax, AUC indices and elimination half life.

Question 3

- Where in the submission documentation is the apparent plasma clearance (CL/F) following extravascular administration results for the nepafenac analyte in Study C-09-053?

Efficacy

Question 4

- The assessment of postoperative pain following cataract surgery was only undertaken as secondary and supportive efficacy endpoints in Study C-09-055, and as supportive efficacy endpoints in Study C-11-003.

Given the current application seeks to register Ilevro for the prevention and treatment of postoperative inflammation and pain following cataract surgery, why did the sponsor not analyse pain as a co-primary endpoint in the pivotal efficacy trials, Studies C-09-055 and C-11-003? Furthermore, why was postoperative pain not analysed as a secondary efficacy endpoint in Study C-11-003?

Question 5

- What proportions of subjects in the intent-to-treat populations, by clinical trial (Studies C-09-055 and C-11-003) and by treatment group, were both cured and pain-free at Day 14?

Safety

Question 6

- Nepafenac 0.3% eye drops suspension was intended to be dosed for 16 days (day prior to surgery, day of surgery, and 14 days following surgery) in the pivotal efficacy studies (C-11-003 and C-09-055) yet more than 43.7% (n = 590 of 1351) total received nepafenac 0.3% treatment for more than 16 days despite the high cure rates and subjects who were pain free at Day 14 post operatively. No explanation is provided why such a large proportion of subjects received nepafenac 0.3% treatment beyond 16 days.

  Will the sponsor please clarify why 43.7% total subjects were exposed to more than 16 days treatment with nepafenac 0.3% eye drops suspension in the pivotal efficacy trials (C-11-003 and C-09-055)?

  What proportions of subjects, by clinical trial (Studies C-09-055 and C-11-003) and by treatment group, who were (a) cured at Day 14 continued treatment beyond Day 14 post-operatively and (b) pain free at Day 14 continued treatment beyond Day 14 post-operatively?

Second round evaluation

- Question 1. Satisfactory response. No amendment to clinical evaluation report.
- Question 2. Satisfactory response. No amendment to clinical evaluation report.
- Question 3. Asked "Where in the submission documentation is the apparent plasma clearance (CL/F) following extravascular administration results for the nepafenac analyte in Study C-09-053?"

  The clinical evaluation report had:

  > *In Study C-09-053, apparent plasma clearance following extravascular administration (CL/F) for the nepafenac analyte was planned but no results were presented. No other estimates of renal clearance were undertaken as part of this application. Nepafenac and its metabolites are primarily eliminated through the renal route, with 85.5% of radiolabelled dose recovered in urine (Study C-04-27 summary Section 18.1.4 pages 58 and 59).*

  The sponsor replied:

  > *The apparent plasma clearance parameter (CL/F) was reported in the clinical study report for C-09-053 (TDOC-0012899). However, this parameter was not explicitly stated in the submission (Module 2.7.2.2 Summary of Pharmacokinetic Results, Table 2.7.2.2-1). Since the dose route was topical ocular and an intravenous study was not conducted, the fraction of dose reaching the plasma compartment is unknown.*

Therefore, reporting this parameter (CL/F) in the submission was considered to be not appropriate.

The sponsor's response was **unsatisfactory** simply stating it was there, not where. This has delayed evaluation.

The sponsor was again asked: "Can the sponsor be asked to be more specific", that is, on which page in the clinical study report for C-09-053 it could be found.

The sponsor's response was satisfactory on this occasion. Amendment made to clinical evaluation report.

- Question 4. Satisfactory response. Amendment made to clinical evaluation report.
- Question 5. Satisfactory response. No amendment to clinical evaluation report.
- Question 6. Satisfactory response. Amendment made to clinical evaluation report.

Second round benefit-risk assessment

Second round assessment of benefits

The first round assessment should be modified by the deletion of:

Areas of uncertainty:

- ~~The efficacy of postoperative pain following cataract surgery has not been fully determined at the time of this report;~~

Second round recommendation regarding authorisation

The first round recommendation should be modified by the deletion of:

- ~~Furthermore, until further data is provided a recommendation for Ilevro to be indicated in the prevention and treatment of postoperative pain associated with cataract surgery should be withheld.~~

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a EU-RMP Version 6.1 (dated 20 September 2013, Data Lock Point 31 July 2012) and Australian Specific Annex (ASA) revision 1 (dated 17 October 2014).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

Table 6: Ongoing safety concerns.

Important identified risks	Corneal disorders: Delayed corneal healing Corneal melt Corneal ulceration Off label use

Important potential risks	Increased ocular bleeding Potential of medication errors Potential interactions: Interaction with topical anti inflammatory steroids Additive effect with benzalkonium chloride Interaction with medicinal products which may prolong bleeding time
Missing information	Long term use of nepafenac Use in patients with concurrent ocular diseases Use in patients using topical ocular medications

RMP evaluator comment

The sponsor notes that "on account of the low systemic absorption of the drug and its active metabolite both known and potential risks are limited to local effects". The sponsor should provide justification for this statement and for not considering systemic absorption as a potential risk.

Otherwise, subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, this summary of ongoing safety concerns is considered acceptable.

Pharmacovigilance plan

The EU-RMP proposes routine pharmacovigilance for all safety concerns. The pharmacovigilance plan also includes the following additional activity:

Table 7: Additional pharmacovigilance activity.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
C12034 Drug Utilisation Study (DUS): cohort study of users of nepafenac and users of other selected ophthalmic NSAIDs in Denmark and the Netherlands	Important identified risk: Off label use	Evaluation of the use of Nepafenac in selected European Populations (Denmark/The Netherlands)	Not provided.

The sponsor has advised in the ASA that two ongoing studies (C-12-067 and C-12-071) to evaluate the safety and efficacy of nepafenac for the improvement in clinical outcomes among diabetic subjects following cataract surgery have been initiated since the data lock point. The sponsor has provided an assurance that information regarding these studies will be included during the next update of the RMP.

RMP evaluator comment

In the Section 31 response, the sponsor should provide an update on the status of proposed drug utilisation study (DUS).

As they are proposed in the pharmacovigilance plan for Australia, relevant milestones for the DUS and the 2 other ongoing studies (C-12-067 and C-12-071) should be provided in the ASA. It should also be made clear in the ASA which safety concerns these activities are assigned to.

The evaluator has no objection to the pharmacovigilance activities proposed. The specified ongoing studies will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. Therefore, it is recommended that interim and final reports are provided to the TGA as appropriate, in accordance with provided milestones.

Risk minimisation activities

The sponsor has concluded in the EU-RMP that routine risk minimisation is sufficient for the safety concerns; however, it appears that additional risk minimisation activities are proposed in the ASA.

RMP evaluator comment

The adequacy of the risk minimisation plan is considered below.

Risk minimisation plan

Routine risk minimisation (that is, product labelling statements) is proposed for all safety concerns.

Additional risk minimisation activities are not specifically proposed in the EU-RMP however the ASA contains the following information:

> *When launched to the Australian market, relevant health professionals will be targeted in a product awareness and training campaign that will include:*
>
> – *Dear Dr Letters*
>
> – *Pharmacy Letters*
>
> – *A Continued Medical Education based education program - Education sessions at symposia/conferences*
>
> – *Provision of Consumer Medicine Information (CMI)*
>
> *As the program is developed, any Australian specific material will be presented to the TGA.*

RMP evaluator comment

The activities described in the ASA (listed above) are considered additional risk minimisation. The sponsor should detail in the ASA which risks the educational program and Dear Healthcare Professional Letters propose to address. As they comprise part of the RMP, educational materials should be provided to the TGA for review.

Routine risk minimisation is proposed for all safety concerns however the sponsor has not included in the ASA which PI statement/s address each safety concern. Therefore it is recommended that the sponsor should provide a table in the ASA which details the Australian-specific risk minimisation for each safety concern (similar to what is provided in the EU-RMP). If the PI statements differ from that proposed in the EU, then justification for any difference should be provided.

The following PI statement under 'Concomitant therapy' emphasises the possibility of delayed healing with the concomitant use of topical NSAIDs and topical steroids:

> *Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may*

> *increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if Ilevro is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.*

However, delayed healing (an identified risk in the nepafenac RMP) can occur with nepafenac treatment with or without concomitant medication use. Therefore, it is recommended to the Delegate that the associated precaution should be revised and retitled such as the following in the US product label:

> *5.2 Delayed Healing*
>
> *Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVROTM (nepafenac ophthalmic suspension), 0.3%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.*

The EU SmPC 'Undesirable effects' includes information on adverse events seen in clinical trials with diabetic patients. Although this relates to the 1 mg/mL concentration, the adverse effects seen in diabetic patients are considered clinically relevant for the 3 mg/mL concentration and such information should be included in the Australian PI.

Otherwise, in regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.

The draft CMI should be revised to as appropriate to correspond to any changes made to the PI as part of the evaluation process.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

For any safety considerations raised by the nonclinical and clinical evaluators, Alcon will provide information that is relevant and necessary to address the issue in the RMP.

The draft PI has been revised to include safety considerations raised by the Non-clinical, Clinical and RMP evaluators (Proposed Australian PI and Package Insert.).

Evaluator's comment

The sponsor's response is acceptable from an RMP standpoint.

Recommendation #2 in RMP evaluation report

In the US, nepafenac is recommended for a shorter post operative time (14 days) than that proposed for Australia (21 days). Further, the US Product label includes the following statement in Warnings and Precautions:

> *Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.*

This statement does not appear in the Australian draft PI and from a risk minimisation perspective the sponsor should provide justification for this disparity.

Sponsor response

The TGA's comment regarding the duration of treatment of Ilevro is noted.

The following statement has been included in the Precautions section of the draft PI:

> *Post marketing experience with topical NSAIDs also suggest that use for more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.*

In addition, the 'Dosage and Administration' section of the draft PI has been revised to reflect the change in duration of treatment. The following statement is proposed:

> *For the prevention and treatment of pain and inflammation, the dose is 1 drop of Ilevro in the conjunctival sac of the affected eye(s) once a day beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 14 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.*

The revised PI is included (Proposed Australian PI and package insert.). The CMI will be revised in alignment with the approved PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #3 in RMP evaluation report

In the header of the EU-RMP, it is stated "Version 8.0" however elsewhere the version is listed as 6.1. The sponsor should confirm the correct version number.

Sponsor response

The discordance is due to the use of an electronic system for handling these documents where every time a new version is made effective the version number in the header rolls out to the following number.

The version of the RMP under evaluation is the version 06.1 (EU-RMP-NEVANAC-06.1) as described throughout the document. This version corresponds to the eighth electronic version (effective date: 20 September 2013).

The applicant did not find the technical possibility to harmonise paper version and electronic versions.

Evaluator's comment

The sponsor's response is noted.

Recommendation #4 in RMP evaluation report

The sponsor notes that

> *on account of the low systemic absorption of the drug and its active metabolite… both known and potential risks are limited to local effects*.

The sponsor should provide justification for this statement and for not considering systemic absorption as a potential risk.

Sponsor response

The sponsor has provided the requested justification (see Section 31 response).

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #5 in RMP evaluation report

In the Section 31 response, the sponsor should provide an update on the status of proposed drug utilisation study.

Sponsor response

The DUS is expected to start at the beginning of the third quarter of 2015. The analysis will be conducted during the third-fourth quarter of 2015. The final study report is expected by the first quarter of 2016.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #6 in RMP evaluation report

As they are proposed in the pharmacovigilance plan for Australia, relevant milestones for the DUS and the 2 other ongoing studies (C-12-067 and C-12-071) should be provided in the ASA. It should also be made clear in the ASA which safety concerns these activities are assigned to.

Sponsor response

The sponsor has provided the requested response (see Section 31 response).

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #7 in RMP evaluation report

The evaluator has no objection to the pharmacovigilance activities proposed. The specified ongoing studies will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. Therefore it is recommended that interim and final reports are provided to the TGA as appropriate, in accordance with provided milestones.

Sponsor response

Alcon agrees to provide the final Clinical Study Reports for the ongoing C-12-067 and C-12-071 clinical trials, as appropriate and relevant when they are available.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #8 in RMP evaluation report

There exists potential for this product to be used off label as treatment for the reduction in the risk of postoperative macula oedema associated with cataract surgery in diabetic patients as this indication is approved elsewhere for a lower strength formulation. If the sponsor sought in the future to register the lower strength product for the macula oedema indication in Australia it is expected that the PI for Ilevro would be revised to make clear that the 0.3% strength is not to be used for that indication.

Sponsor response

As requested by the TGA, the following statement has been included in the Precautions section of the PI:

> *Ilevro should not be used for the reduction in the risk of postoperative macular oedema associated with cataract surgery as efficacy and safety of this strength for this indication has not been studied.*

The revised PI is included (Proposed Australian PI and package insert.). The CMI will be revised in alignment with the approved PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #9 in RMP evaluation report

The activities described in the ASA (listed above) are considered additional risk minimisation. The sponsor should detail in the ASA which risks the educational program and Dear Healthcare Professional Letters propose to address as risk minimisation. As they comprise part of the RMP, educational materials should be provided to the TGA for review.

Sponsor response

Educational materials proposed for Australia are currently not available. Alcon provides the assurance that educational materials will be provided to the TGA prior to launch of the proposed product in Australia.

Evaluator's comment

The sponsor's commitment to provide the TGA with educational materials prior to product supply in Australia is noted.

As they comprise a key component of the risk minimisation plan, these materials, when provided, will be reviewed for their utility as additional risk minimisation activities. The sponsor should specify which risks are assigned to these activities in the ASA.

Recommendation #10 in RMP evaluation report

Routine risk minimisation is proposed for all safety concerns however the sponsor has not included in the ASA which PI statement/s address each safety concern. Therefore it is recommended that the sponsor provide a table in the ASA which details the Australian specific risk minimisation for each safety concern (similar to what is provided in section II.5 Summary of the EU-RMP). If the statements differ from that proposed in the EU then justification for any difference should be provided.

Sponsor response

A table which details the Australian specific risk minimisation for each safety concern and any differences from that proposed in the EU SmPC is provided in the ASA. If the statement differs from that proposed in the EU, then a justification for the difference is also provided. The revised ASA is included.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #11 in RMP evaluation report

The following statement under 'Concomitant therapy' emphasises the possibility of delayed healing with the concomitant use of topical NSAIDs and topical steroids:

> *Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if Ilevro is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.*

However delayed healing (an identified risk in the nepafenac RMP) can occur with nepafenac treatment with or without concomitant medication use. Therefore, it is recommended to the Delegate that the associated precaution should be revised and retitled such as the following in the US Product label:

> *5.2 Delayed Healing*
>
> *Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including Ilevro (nepafenac ophthalmic suspension), 0.3%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.*

Sponsor response

As requested by the TGA, the section related to delayed healing has been re-titled in the 'Precautions' section of the PI.

The revised PI is included (Proposed Australian PI and package insert.). The CMI will be revised in alignment with the approved PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Recommendation #12 in RMP evaluation report

The EU SmPC section 'Undesirable effects' includes information on AEs seen in clinical trials with diabetic patients. Although this relates to the 1 mg/mL concentration, the adverse effects seen in diabetic patients are considered clinically relevant for the 3 mg/mL concentration and such information should be included in the Australian PI

Sponsor response

As requested by the TGA, the following statement has been included in the PI:

> *Diabetic patients*
>
> *In the two clinical studies involving 209 patients, diabetic patients were exposed to Nepafenac 1 mg/mL eye drops, suspension treatment for 60 days or greater for the prevention of macular oedema post cataract surgery. The most frequently reported adverse reaction was punctate keratitis which occurred in 3% of patients, resulting in a frequency category of common. The other reported adverse reactions were corneal epithelium defect and allergic dermatitis which occurred in 1% and 0.5% of patients, respectively both adverse reactions with a frequency category of uncommon.*

The revised PI is included (Proposed Australian PI and package insert.). The CMI will be revised in alignment with the approved PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

Educational materials

The sponsor's commitment to provide the TGA with educational materials prior to product launch in Australia is noted. The TGA will review the educational materials (including Dear Healthcare Professional Letter) as part of the RMP evaluation once these are provided.

Safety specification recommendations

The clinical and nonclinical evaluation reports included recommendations regarding the RMP safety specification. The sponsor's response to these is acceptable from an RMP perspective. The updated RMP/ASA incorporating the commitments made in the Section 31 response should be submitted to the TGA.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Advice from the ACSOM was not sought for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

The Safety Specification in the draft RMP is not entirely satisfactory and should be revised, having regard to the comments below:

- In the 'Potential for overdose' section, the sponsor has provided dose/kg values based on Nevanac, the 0.1% nepafenac eye drop preparation instead of the proposed 0.3% nepafenac preparation in which 9 mg is available in a 3 mL fill bottle, which gives rise to 0.45 mg/kg if a 20 kg child fully ingests the contents of a 3 mL bottle. This dose equates to 11% to 45% of the adult dose. Hence, the exposure to the 20 kg child is approximately double that for the 0.1% preparation. This should be reflected in the RMP.
- Further, up to 45% of the maximum adult dose is not insignificant. The equivalent data for Voltaren Ophtha is 3% of the maximum adult dose (see Australian PI). Hence, the risk of NSAID induced toxicity in oral ingestion for Ilevro is up to 15 times greater than that with Voltaren Ophtha. It is noted that 'overdosage' is not included in the summary of safety concerns and this should be revisited.
- Pregnancy and breast feeding are not included in the RMP summary of safety concerns and their inclusion should be reconsidered as 'Missing Information' items.
- Concomitant administration with topical ocular prostaglandin analogues (for example, leading to an increase in IOP) is not included as an important potential risk. This should be reviewed.

RMP evaluator comment

The sponsor has responded to the clinical evaluator's safety specification comments (Section 31 response). The updated RMP/ASA incorporating the commitments made in the response should be submitted to the TGA.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for nepafenac detailed in the sponsor's draft RMP are in general concordance with those of the Nonclinical Evaluator. However, the exposure ratios are inaccurate for Ilevro as they appear to have been based on human dosing with 0.1% nepafenac. While the safety margins are lower based on nepafenac alone, the exposure ratios should be calculated for the sum of nepafenac and its active metabolite, amfenac. Therefore, the safety margins in pregnant rats and rabbits should be ≥155 and ≥135, respectively, based on Cmax and AUC values derived from the sum of nepafenac and amfenac, and human values determined after once daily topical ocular dosing with 0.3% nepafenac.

RMP evaluator comment

The sponsor has acknowledged the nonclinical comments and has proposed to make the requested modifications at the next revision of the RMP and submit that revision to the TGA (Section 31 response).

Key changes to the updated RMP

ASA revision 1 (dated 17 October 2014) has been superseded by ASA revision 2 (dated 29 May 2015) (Table 8).

Table 8: Summary of key changes between ASA revision 1 and ASA revision 2.

Summary of key changes between ASA revision 1 and ASA revision 2	
Pharmacovigilance activities	More detail included regarding the pharmacovigilance activities as they apply to Australia.
Risk minimisation activities	A table summarising the risk minimisation activities for Australia and comparing them with the EU SmPC has been included.

RMP evaluator comment

The evaluator has no objection to the above changes.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *The EU RMP version 6.1 (dated 20 September 2013, DLP 31 July 2012) and ASA revision 2 (dated 29 May 2015) to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The chemical, pharmaceutical and biopharmaceutic aspects of the application are complete and satisfactory.

The chemistry evaluator has noted that since the drug substance exhibits minimal aqueous solubility, the finished product has been developed as a suspension. Particle size is an important parameter and is controlled in the finished product specifications at the intermediate stage 1 part of the manufacture and also in the final specifications.

Nonclinical

There are no nonclinical objections to approval of nepafenac eye drops suspension for the indication proposed.

The nonclinical evaluator has noted that nepafenac and its pharmacologically active metabolite, amfenac, both inhibit COX-1 and to a lesser extent COX 2. Nepafenac was converted to amfenac in anterior and posterior ocular tissues. When compared directly, nepafenac was a more potent COX inhibitor than amfenac. Topical ocular administration

rapidly inhibited ex vivo prostaglandin synthesis in the iris/ciliary body (ICB) and retina/choroid tissues, with PGE2 synthesis in ICB inhibited by ≥57% for up to 24 h. In vivo, topical ocular nepafenac inhibited trauma induced PGE2 accumulation in aqueous humour and breakdown of the blood-aqueous barrier.

Secondary PD studies showed that nepafenac inhibited choroid and preretinal revascularisation in rodents and rabbits, and rodent models of oxygen induced retinopathy. Nepafenac also attenuated diabetes induced retinopathy but not retinal permeability.

Safety pharmacology studies did not identify any specific risks of nepafenac, but studies were not GLP compliant. In vitro cardiovascular safety studies were not conducted with nepafenac. However, GLP compliant in vitro and in vivo studies of amfenac did not identify any adverse cardiovascular effects at concentrations up to 88× (in vitro) and >10,000× (in vivo) the clinical Cmax for amfenac.

The repeat dose studies identified NSAID class effects, but these are unlikely to occur clinically at the low systemic exposure. At very high relative exposures adverse corneal effects were observed in rats (opacity and mineralisation). Consistent with known NSAID effects, nepafenac is maternally toxic and teratogenic in animal studies, but only at very high relative exposures. The proposed Pregnancy Category C was considered to be appropriate based on the nonclinical findings, and is consistent with other NSAIDs.

Clinical

Pharmacology

Nepafenac is a prodrug that penetrates the cornea and is rapidly converted to the active, amfenac by intraocular hydrolases. Bioavailability of either nepafenac or amfenac was not examined in this submission. PK studies demonstrated that both nepafenac and amfenac are present in plasma after ocular administration and that there is a positive relationship between dose and plasma concentration. The tmax of nepafenac in plasma was reached at approximately 0.5 h and for amfenac in approximately 0.75 h after topical administration to the eye. The sponsor has proposed a pre operative dose at 30 to 120 minutes prior to surgery. This timing should result in a maximum or near maximum concentration of active drug within the eye at commencement of surgery. The half life in serum is <1 h, though the sponsor is claiming a duration of action in the eye of > 24 h. That claim is consistent with nonclinical data.

Amfenac undergoes extensive hydroxylation of the aromatic ring, which leads to glucuronide conjugate formation. Following metabolic conversion to glucuronides with 9 quantifiable aglycone metabolites identified in plasma. Subsequent clearance is predominantly renal.

Following oral administration of 14C nepafenac (Study C-04-27), 91.7% of radioactivity was recovered, with 85.5% and 6.2% recovered in urine and faeces, respectively. As would be anticipated with an eyedrop, inter-individual variability was moderate to high across the PK studies. Within subject variability does not appear to have been examined.

No clinical pharmacodynamic studies were submitted. No QT study was performed and there were no drug interaction studies. As noted by the clinical evaluator, pharmacokinetic drug interactions are unlikely to occur and if they occur are unlikely to be clinically significant given the lack of effect of nepafenac and amfenac on hepatic cytochrome P450 enzymes, and the low systemic exposure of nepafenac and amfenac.

On the basis of limited systemic exposure of topical nepafenac 0.3% eye drops, no dose adjustments would be expected for subjects with impaired hepatic or renal function, or by gender or age.

Efficacy

No clinical dose finding studies were performed for this submission. Dose selection for the nepafenac 0.3% solution was based on nonclinical studies and clinical trials supporting authorisation of the nepafenac 0.1% product in other regulatory jurisdictions.

During the clinical development of nepafenac, patients were exposed to various formulations with concentrations ranging from 0.003% to 0.3% for up to 6 months. In a pharmacokinetic animal model, nepafenac 0.3% dosed once daily resulted in steady-state drug levels (nepafenac and amfenac) in the ICB that were significantly higher than those for nepafenac 0.1% when dosed once daily or 3 times daily. The once daily formulation had similar cumulative exposure levels over a 24 h period to those observed with nepafenac 0.1% dosed 3 times daily.

A pivotal Phase III study, C-09-055 and a Phase II study, C-11-003 are described in the clinical evaluation report. These studies had similar designs and the same inclusion and exclusion criteria. Both were randomised, double blind, active and vehicle controlled studies with exposure to nepafenac 0.3% once daily pre operatively and for up to 14 days post operatively.

Study C-09-055 had 4 study arms: nepafenac 0.3% given once daily, nepafenac 0.1% given three times daily, nepafenac vehicle 0.3% given once daily and nepafenac vehicle 0.1% given three times daily. Patients were randomised 4:1 to nepafenac 0.3% or nepafenac vehicle 0.3%, and 4:1 to nepafenac 0.1% or nepafenac vehicle 0.1%. Patients began study medication the day prior to surgery and took their medication on the day of surgery and for 2 weeks following surgery. An additional dose (one drop) of study medication was administered 30-120 minutes prior to surgery. Only one eye of each patient was exposed to either nepafenac or vehicle during the study. Post operative assessments were performed on Days 1, 3, 7 and 14 after surgery.

The primary efficacy objectives of C-09-055 were to demonstrate:

- Nepafenac 0.3% dosed once daily is noninferior to nepafenac ophthalmic suspension, 0.1% (Nevanac) dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to nepafenac vehicle 0.3% dosed once daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nepafenac 0.1% dosed 3 times daily is superior to nepafenac vehicle 0.1% dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

Both studies enrolled adult patients requiring cataract surgery by phacoemulsification and implantation of a posterior chamber intraocular lens. Exclusion criteria were intended to ensure that patients had no baseline inflammation and that they did not receive any anti inflammatory medication other than the assigned therapy. Notable exclusion criteria were:

- Use of topical ocular, inhaled or systemic NSAIDs within 7 days of surgery and through study exit, with the exception low dose of aspirin;
- Use of topical ocular, inhaled or systemic steroids within 14 days prior to surgery and through study exit;

- Any intraocular inflammation (aqueous cells or flare greater than Grade 0) or ocular pain greater than Grade 1 in the study eye that was present during the Baseline visit;
- A history of chronic or recurrent inflammatory eye disease (for example, iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) in the operative eye;
- Patients who in the opinion of the investigator were at increased risk of developing postoperative macular oedema in the operative eye (for example, diabetic retinopathy patients).

The primary efficacy measure in Study C-09-055 was the proportion of patients with a cure at Day 14. Cure was defined as a score of 0 for both aqueous cells and flare. The secondary efficacy measure was the proportion of patients who were pain free as assessed by the Investigator at Day 14. Pain free was defined as a score of 0 on the Investigator rating scale which ranged from 0 (none) to 5 (severe).

For the comparison of active versus vehicle treatment groups, the proportion of patients who were cured was compared between pairs of treatment groups (nepafenac 0.1% versus nepafenac vehicle 0.1%; nepafenac 0.3% versus nepafenac vehicle 0.3%) using the

Each Cochran-Mantel-Haenszel test was reported at the 5% significance level, two sided. Stratification for Investigator was used in the Cochran-Mantel-Haenszel test to match stratification used in the randomisation process. The comparisons of active to vehicle were reported using only the vehicle group with the same dosing frequency.

Analysis of the Investigator's assessment of ocular pain was analogous to the analyses described above for the primary endpoint. Comparisons of the active groups with the vehicle groups were reported using only the vehicle group with the same dosing schedule to assess assay sensitivity and the efficacy of the investigational product.

A total of 2022 patients were randomised to treatment. Mean (standard deviation [SD]) age was 68.9 (9.22) years with 28.7% of the study population aged ≥ 75 years. Cure at Day 14 (ITT analysis) was reported for 552 (68.4%) patients given nepafenac 0.3%, 568 (70.0%) given nepafenac 0.1%, 67 (34.0%) given nepafenac vehicle 0.3% and 73 (35.6%) given nepafenac vehicle 0.1%. The non inferiority comparison between the two nepafenac concentrations is not relevant. Superiority of nepafenac 0.3% to nepafenac vehicle 0.3% for cure at Day 14 was demonstrated ($p < 0.0001$).

Ocular pain was a secondary efficacy variable. At Day 14 734 (91.0%) of patients given nepafenac 0.3%, 737 (90.9%) given nepafenac 0.1%, 98 (49.7%) given nepafenac vehicle 0.3% and 115 (56.1%) given nepafenac vehicle 0.1% were pain free. Nepafenac 0.3% was superior to nepafenac vehicle 0.3% for the proportion of patients who were pain free at Day 14 ($p< 0.0001$). The results for the cumulative percentage of pain free patients were also analysed at each study visit. Statistically significant differences, favouring nepafenac 0.3% compared to its vehicle were observed in the cumulative percentage of patients who were pain-free at each of the postoperative visits ($p < 0.0001$).

In C-11-003 patients were randomised in a 2:2:1 ratio to receive treatment with nepafenac 0.3%, nepafenac 0.1%, or nepafenac vehicle 0.3%, respectively. Each study treatment was given once daily with an additional dose administered between 30-120 minutes prior to surgery. The primary objective was to demonstrate the superiority of nepafenac 0.3% to its vehicle in the prevention and treatment of pain and inflammation associated with cataract surgery at Day 14.

The primary efficacy endpoint was cure at Day 14 with cure defined as a score of 0 for both aqueous cells and flare, where the 5 unit aqueous cells score ranged from 0 (none) to 4 (>30 cells), and the 4 unit aqueous flare score ranged from 0 (No visible flare when compared with the normal eye) to 3 (severe – very dense flare). Pain was a supportive variable, assessed as the percentage pain free at each visit. It was possible for a patient to

be considered a treatment failure for ocular pain and still have zero cells and zero flare; therefore, patients with a pain scores of 4 or greater were not considered to be a cure even if they had a cells score + flare score = 0.

A total of 1257 patients were randomised. Mean (SD) age was 69.0 (9.24) years with 30% of the study population aged ≥ 75 years. Cure at Day 14 was reported for 331 (64.6%) patients given nepafenac 0.3%, for 322 (65.3%) given nepafenac 0.1% and for 63 (25%) given nepafenac vehicle 0.3%. Nepafenac 0.3% was superior to its vehicle for cure at Day 14 ($p < 0.0001$). The cumulative percentage of patients who were pain free at Day 14 was 89.1% for nepafenac 0.3%, 89.0% for nepafenac 0.1% and 40.1% for nepafenac vehicle 0.3%. Nepafenac 0.3% was superior to its vehicle for the percentage of patients pain free on each of the days assessed (days 1, 3, 7 and 14 post-operatively), $p < 0.0001$ for each comparison).

Safety

The primary safety analysis was of patients enrolled in Studies C-11-003 and C-09-055. A total of 3324 patients were assessed for safety in these studies and 1351 patients received at least one dose of nepafenac 0.3%. In Study C-09-055, the mean (SD) duration of treatment with nepafenac 0.3% was 16.3 ± 3.3 days (range 2 to 30 days) compared to a mean (SD) duration of 12.0 ± 5.6 days (range 2 to 20 days) for nepafenac vehicle 0.3% treatment. In Study C-11-003, the mean (SD) duration of nepafenac 0.3% treatment was 14.9 ± 3.7 days (range 1 to 23 days) compared to a mean duration (SD) of 10.3 ± 5.7 days (range 1 to 23 days) for nepafenac vehicle 0.3%.

No deaths were attributed to exposure to nepafenac in any studies. Twelve patients given nepafenac 0.3% experienced SAEs, these are discussed in the clinical evaluation report. None of these events were attributed to nepafenac. Discontinuation rates in the pivotal studies were higher in patients given placebo compared with active treatment with either nepafenac 0.3% or 0.1%. Reasons for study discontinuation are shown. In both studies the most frequent reason for early discontinuation from study was inadequate efficacy.

All ADRs reported in the post cataract inflammation studies (C-09-055 and C-11-003) were single reports. Three ADRs were reported in the nepafenac 0.3% treatment group and none in the nepafenac 0.1% treatment group. The 3 ADRs were: eye pain and punctate keratitis which were mild in intensity, resolved without treatment and did not interrupt study participation, and hypersensitivity (characterised as an allergic reaction localised on the face) was moderate in intensity, resolved with treatment (Opcon A) and caused the patient to discontinue from the study.

All other ADRs reported for patients in the post cataract inflammation studies occurred in the nepafenac vehicle 0.3% treatment group (single reports of eyelid oedema and foreign body sensation in eyes) and in the nepafenac vehicle 0.1% treatment group (single report of eye pain). The eyelid oedema and foreign body sensation in eyes were moderate and mild in intensity, respectively, and both events resolved without treatment and did not interrupt patient study participation. The eye pain was moderate in intensity, resolved without treatment and did not interrupt patient study participation.

Risk management plan

The RMP evaluator has recommended that the proposed indication be restricted to non-diabetic subjects only at this time until the results from clinical trials such as Studies C-12-067 and C-12-071, have been completed and evaluated as part of a submission for extension of indications for nepafenac (Ilevro).

Two new clinical studies (C-12-067 and C-12-071) to evaluate the safety and efficacy of nepafenac (Ilevro) for the improvement in clinical outcomes among diabetic subjects

following cataract surgery, have been initiated since the DLP of the current RMP. These studies, primarily conducted to support a new/expanded indication in the US, EU and other regions, are currently ongoing and routine ongoing monitoring of masked safety data has not identified any new/previously unknown risks for Ilevro. Information regarding these studies will be included during the next update of the RMP. A 60 day treatment period has been proposed.

The RMP evaluator notes that the following wording was proposed by the sponsor in the RMP for the EU SmPC for Nevanac:

> *[Ilevro] 3 mg/ml eye drops, suspension should not be used for the reduction in the risk of postoperative macular oedema associated with cataract surgery as efficacy and safety of this strength for this indication has not been studied.*

The RMP evaluator recommended that a similar statement should be included in the 'Indications' section of the Australian PI or, at the very least, a similar statement in the 'Precautions' section.

Risk-benefit analysis

Delegate's considerations

The data package to support registration of nepafenac 0.3% eye drop suspension in Australia was initially the same as the package submitted to the EMA. A nepafenac 0.1% eye drop suspension had been given marketing authorisation in the EU previously so this was essentially a new strength and dose regimen application for the EMA however nepafenac is a new chemical entity for Australia and additional pharmacokinetic data were subsequently obtained from the sponsor.

Few pharmacology studies were submitted. Given the low systemic exposure and the metabolic pathway of the prodrug, nepafenac and the active, amfenac, this minimal pharmacology data are accepted. The sponsor has claimed that the duration of action of this product at the cornea is >24 h. There were no clinical pharmacology studies that support that claim however nonclinical studies support this claim. No dose adjustment is needed for concurrent medicines due to interactions or for patients with impaired renal or hepatic function.

The pivotal efficacy and safety studies were designed with the assumption that the 0.1% nepafenac eye drop was an appropriate active comparator. This is not the case in Australia where the 0.1% eye drop is available only as an unregistered medicine. Thus the relevant efficacy and safety comparator in both efficacy and safety studies is the nepafenac vehicle 0.3%. Nepafenac 0.3% was superior to its vehicle in reducing ocular inflammation and pain at Day 14 post cataract surgery. Only exploratory analyses were performed prior to Day 14 however these suggested a reduction in pain and inflammation superior to vehicle from Day 1 post surgery.

The nepafenac 0.1% comparisons were supportive of the overall efficacy of nepafenac in reducing post operative inflammation and pain following cataract surgery.

The relative efficacy of nepafenac 0.3% against any other NSAID eye drop has not been assessed. The sponsor had initially proposed use of nepafenac 0.3% for up to 21 days following cataract surgery and use with other topical medications including ointments. The clinical studies assessed efficacy only to Day 14 post surgery and without use of other ocular or systemic anti inflammatory products other than low dose aspirin. The PI was subsequently amended to reflect the reduced duration of treatment. It is likely that use of additional anti inflammatory products such as corticosteroids would also have reduced

inflammation and made differences between nepafenac and its vehicle smaller. This is likely to be the reason these medicines were not permitted in the efficacy studies.

The clinical evaluators have noted that patients with diabetic retinopathy were excluded from the studies assessing efficacy and safety of nepafenac and recommended that the indications or Precautions sections of the PI note that this product should be used in non diabetic subjects only at this time until the results from clinical trials in these groups have been completed and evaluated as part of a submission for extension of indications for Ilevro. The Delegate considers this is an inappropriate restriction. Patients with diabetes were excluded from the efficacy and safety studies due to the higher risk of post operative complications which may have required preventative treatments that were prohibited as they would have masked the efficacy of nepafenac. Patients with diabetes are a major subgroup of patients with cataract and should not be excluded from use of nepafenac on the basis of their exclusion from the pivotal efficacy and safety studies. At this time, the Delegate considers that it is sufficient to include a statement that patients with diabetic retinopathy were excluded from the pivotal studies in the description of those studies in the 'Clinical Trials' section of the PI. The 'Precautions' section has been amended to include a statement to the effect that efficacy and safety of nepafenac 0.3% has not been examined in patients with diabetic retinopathy.

Proposed action

The Delegate has no reason to say, at this time, that the application for Ilevro should not be approved for registration subject to negotiation of the PI.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- The sponsor has proposed an indication that does not specify a patient group. In the EU, the indications for 1% nepafenac specify adults.

  In Australia, the indications for both Acular and Voltaren eye drops do not specify use in adults. The committee is requested to provide advice on whether the indications should be restricted to adults.

- Does the committee consider that it is appropriate to amend the indications to exclude patients with diabetes?

- Does the committee consider that the 'Dosage and Administration' of 0.1% nepafenac should be limited to 14 days?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application

Response from sponsor

Delegate's issue 1

- Whether it is appropriate to specify in the indications that this product should be used in adults only.

Sponsor response

Alcon supports the appropriateness of this issue to specify a patient group in the Indication to reflect the submitted clinical data. In addition to the Delegate's request of adding 'in adults', Alcon proposes to specify 'the elderly' as a patient group. The rationale being that the two safety and efficacy studies, C-09-055 and C-11-003, were conducted in

adults (18-64 years) and elderly (65 years and over), based on ICH definitions. Over 73% of patients in the ITT dataset of these studies were elderly (65 years or older).

Therefore, Alcon is proposing the revised indication:

> *The prevention and treatment of postoperative pain and inflammation associated with cataract surgery* ***in adults and elderly****.*

Delegate's issue 2

- Whether patients with diabetes should be excluded from use of the product.

Sponsor response

Alcon agrees with the Delegate's justification for not restricting the use of Ilevro to nondiabetic patients.

Patients with diabetic retinopathy were excluded from the efficacy and safety studies since they have a higher risk of developing post operative macular oedema especially if they do not receive any anti inflammatory coverage pre and post surgery. Anti inflammatory medications except low dose aspirin were disallowed due to the potential for confounding effects on study variables and thus these patients were excluded due to the higher risk. However, it should be noted that diabetic patients without any retinopathies were not excluded. No safety concerns were identified for Nepafenac 0.3% after dosing for 14 days following cataract surgery in these studies overall study populations based upon a review of adverse events and ocular safety parameters.

A statement has been added that patients with diabetic retinopathy were excluded from the pivotal studies in the description of those studies in the 'Clinical Trials' section of the PI.

Additionally, since the efficacy and safety of Nepafenac 0.3% for the reduction in risk of post operative macular oedema in diabetic patients with a longer treatment regimen is still being evaluated, a statement addressing this is included in the 'Precautions' section of the PI:

> *Ilevro should not be used for the reduction in the risk of postoperative macular oedema associated with cataract surgery as efficacy and safety of this strength for this indication has not been studied.*

Delegate's issue 3

- Whether the duration of use should be limited to the duration of use in the clinical trials.

Sponsor response

As agreed in Alcon's Section 31 response dated 29 May 2015, the 'Dosage and Administration' section of the PI has been amended to reduce the duration of use from 21 days to 14 days. The annotated and clean copy of the PI and CMI is included.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ilevro lyophylised powder for reconstitution containing 0.3% of nepafenac to have an overall positive benefit-risk profile for the indication:

> *The prevention and treatment of postoperative pain and in/lamination associated with cataract surgery.*

In making this recommendation, the ACPM:

- Was of the view that no age restriction was necessary.
- It was unreasonable to restrict use to non diabetics.
- Duration of treatment could be left to the discretion of the physician.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and specifically advised on the inclusion of the following:

- A 'Contraindication' for the use of soft contact lenses with Ilevro as the benzalkonium chloride preservative in Ilevro may be absorbed by these lenses.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- The sponsor has proposed an indication that does not specify a patient group. In the EU the indications for 1% nepafenac specify adults. In Australia, the indications for both Acular and Voltaren eye drops do not specify use in adults. The committee is requested to provide advice on whether the indications should be restricted to adults.

The ACPM noted the sponsor's pre ACPM response which proposed a revised indication restricting use to adults and the elderly. The ACPM was of the view that it was not necessary to include an age restriction in the indication. However, the PI should note the lack of studies in lactation and in children.

- Does the committee consider that it is appropriate to amend the indications to exclude patients with diabetes?

The ACPM noted the sponsor's pre ACPM response which stated that patients with diabetic retinopathy were excluded from the efficacy and safety studies since they had a higher risk of developing post operative macular oedema, especially if they did not receive any anti inflammatory coverage pre and post surgery. However, diabetic patients without any retinopathies were not excluded and there were no safety concerns identified for nepafenac 0.3% after dosing for 14 days following cataract surgery in these studies.

The ACPM advised that patients with diabetes should not be excluded from the indication on the basis of their exclusion from the pivotal efficacy and safety studies as many diabetics require cataract surgery. However, the PI should include a statement that patients with diabetic retinopathy were excluded from the pivotal studies in the description of those studies in the 'Clinical Trials' section of the PI.

The ACPM noted that the 'Precautions' section had been amended to include a statement that Ilevro should not be used for the reduction in the risk of postoperative macular oedema associated with cataract surgery as efficacy and safety of this strength for this indication have not been. The results of current trials in diabetics should also be provided when available.

- Does the committee consider that the 'Dosage and Administration' of 0.1% nepafenac should be limited to 14 days?

The ACPM noted that the sponsor had agreed to limit the duration of treatment to 14 days instead of 21 days. The ACPM advised that the treatment duration did not necessarily have to be that used in the clinical trials and could perhaps be left to the discretion of the physician.

The ACPM advised that the use of soft contact lenses with Ilevro should be contraindicated because the benzalkonium chloride preservative in Ilevro may be absorbed by these lenses.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ilevro (nepafenac) 0.3% eye drops, suspension, bottle indicated for:

> *The prevention and treatment of postoperative pain and inflammation associated with cataract surgery*

Specific conditions of registration applying to these goods

- The Ilevro nepafenac EU RMP, version 6.1 (dated 20 September 2013, DLP 31 July 2012) and ASA revision 2 (dated 29 May 2015) to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Ilevro at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au