



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 December 2010

NEVANAC 1mg/ml, eye drops, suspension
B/1 (CIP code: 383 939-3)

Applicant: ALCON

nepafenac
ATC code: S01BC10

List I

Date of Marketing Authorisation (centralised European): 11 December 2007

Reason for request: Inclusion on list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Nepafenac¹

Excipient: benzalkonium chloride.

1.2. Indication

“Prevention and treatment of postoperative pain and inflammation associated with cataract surgery”.

1.3. Dosage

Use in adults, including the elderly

“The dosage is one drop in the conjunctival sac of the affected eye(s) 3 times daily, beginning 1 day prior to cataract surgery, continued on the day of surgery and for the first 2 weeks of the postoperative period. Treatment can be extended to the first 3 weeks of the postoperative period, as directed by the clinician. An additional drop should be administered 30-120 minutes prior to surgery.”

Paediatric patients

NEVANAC is not recommended for use in children below 18 years due to a lack of data on tolerance and efficacy.

Use in hepatic and renal impairment

NEVANAC has not been studied in patients with hepatic disease or renal impairment. It is eliminated primarily through biotransformation and the systemic exposure is very low following administration. No dosage adjustment is warranted in these patients.

Methods of administration

“For ocular use. Instruct the patient to shake the bottle well before use. If more than one type of eye drop is being used, they must be administered at least 5 minutes apart. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct the patient to keep the bottle tightly closed when not in use.

¹ Nepafenac is a non-steroidal anti-inflammatory and an analgesic. It is a prodrug: after ocular dosing, it is converted by ocular tissue hydrolases to amfenac. Most of the hydrolytic conversion takes place in the retina/choroid, subsequently in the iris/ciliary body and the cornea, in conjunction with tissue vascularisation. Amfenac, a non-steroidal anti-inflammatory, inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2010):

S: Sensory organs
S01: Ophthalmologicals
S01BC: Non-steroidal anti-inflammatory agents
S01BC10: Nepafenac

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines: other non-steroidal anti-inflammatory eye drops indicated for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery:

- ACULAR 0.5% eye drops supplied in bottles (preservative: benzalkonium chloride) (ketorolac tromethamine)
- VOLTARENE 0.1% eye drops supplied in single-dose packs (no preservative) and DICLOCED 0.1% eye drops supplied in bottles (preservative: boric acid); (diclofenac)
- INDOCOLLYRE 0.1% supplied in single-dose packs (no preservative) and bottles (preservative: sodium mercuriothiolate or thiomersal) (indomethacin)
- OCUFEN 0.03% supplied in single-dose packs (no preservative) (flurbiprofen)

2.3 Medicines with a similar therapeutic aim

- Anti-inflammatory eye drops containing a corticosteroid (FLUCON, VEXOL) or a corticosteroid and an antibiotic (FRAKIDEX, MAXIDROL, TOBRADEX)

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy data

The clinical dossier is based on the results of two dose-finding studies and four randomised comparative studies conducted to assess the efficacy and tolerance of the ophthalmic suspension NEVANAC (nepafenac). The two dose-finding studies showed that the two dose levels of nepafenac (0.3 mg/ml and 1 mg/ml) have similar effects on inflammation. However, the phase III studies were carried out with the 1 mg/ml dose².

The pharmaceutical company has submitted the findings of a study versus placebo (C-03-32) and of a study versus placebo and ketorolac tromethamine (C-04-65) in support of its application.

Study versus placebo

Methodology

Protocol	Methodology	Population	Treatment	Dosage	Duration of treatment
C-03-32 (N = 490)	Double-blind, randomised, controlled parallel-group study	Patients aged 18 or over scheduled for cataract surgery with implantation of an intraocular lens	<ul style="list-style-type: none">• NEVANAC 1 mg/ml• PLACEBO	<ul style="list-style-type: none">• 1 drop three times a day• 1 drop three times a day	16 days

Dosage: 1 drop of NEVANAC 1 mg/ml eye drop in suspension or of placebo was administered three times a day, the day before cataract surgery, on the day of surgery and 14 days after surgery. An additional drop was administered before the surgery. Check-ups were conducted one day (D1), three days (D3), seven days (D7) and fourteen days (D14) after surgery.

The Primary efficacy endpoint of the study was the percentage of healing (inflammatory cells + erythema score = 0) at the check-up carried out on D14. The basis on which the efficacy of the proprietary drug was assessed was therefore the number of inflammatory cells and the severity of erythema, markers for ocular inflammation. The number of inflammatory cells was assessed by the investigator using a slit lamp on a five-point scale (0 = no inflammatory cells to 4 = more than 30 inflammatory cells), and the severity of erythema was assessed on a four-point scale (0 = no visible erythema to 3 = very severe erythema).

The percentage of patients experiencing no eye pain³ was a secondary endpoint.

Study results

The efficacy of NEVANAC 1 mg/ml eye drop suspension was assessed on 476 patients (243 receiving NEVANAC 1 mg/ml eye drop suspension and 233 receiving placebo) for intention-to-treat analyses. On D14 the percentage of healing was higher for NEVANAC 1 mg/ml (62.6%) than for placebo (17.2%), $p < 0.0001$, ITT.

Furthermore, the percentage of patients reporting no eye pain in any post-operative check-ups was higher for NEVANAC 1 mg/ml than for placebo ($p < 0.0001$).

² See EMA assessment report: p. 20/39 of the EPAR.

³ Eye pain was assessed by the investigator on a six-point scale (from 0 = none to 5 = severe) according to the following criteria: feeling of having something in the eye, including the feeling that a foreign body is present, stabbing pain.

Study versus placebo and versus ketorolac tromethamine

Methodology

Protocol	Methodology	Population	Treatment	Dosage	Duration of treatment
C-04-65 (N = 227)	Double-blind, randomised, controlled parallel-group study	Patients aged 18 or over scheduled for cataract surgery with implantation of an intraocular lens	<ul style="list-style-type: none">• NEVANAC 1 mg/ml (N = 77)• Ketorolac 5 mg/ml (N = 73)•	<ul style="list-style-type: none">• 1 drop three times a day• 1 drop three times a day• 1 drop three times a day	23 ± 2 days

Dosage: 1 drop of NEVANAC 1 mg/ml, ketorolac 5 mg/ml or of placebo was administered three times a day, the day before cataract surgery, on the day of surgery and 3 weeks after surgery. An additional drop was administered 30 to 120 minutes prior to surgery. Check-ups were conducted one day (D1), three days (D3), seven days (D7), fourteen days (D14), 21 days (D21) and 28 days (D28) after surgery.

The primary aim of this study was to demonstrate the superiority of NEVANAC 1 mg/ml eye drop suspension to placebo, and the non-inferiority of NEVANAC 1 mg/ml eye drop suspension to ketorolac 5 mg/ml.

The Primary efficacy endpoint was the superiority of NEVANAC 1 mg/ml versus placebo in terms of the percentage of healing (inflammatory cell score = 0 and erythema score = 0) at the check-up on D14.

The secondary efficacy endpoints assessed included:

- Non-inferiority of NEVANAC 1 mg/ml to ketorolac 5 mg/ml in respect of the average inflammatory cells + erythema score on D21.
- Comparison of NEVANAC 1 mg/ml eye drop suspension with ketorolac 5 mg/ml in respect of:
 - the percentage of patients in whom treatment failed (based on the inflammatory cells, erythema and eye pain scores),
 - the percentage of patients with no eye pain (assessed by the investigator),
 - assessment of discomfort during administration (feeling of burning, stinging) by the patient on D7 on a five-point scale (from 0 = none to 4 = very severe).

Study results

Efficacy results were obtained for 225 of the 227 patients who took part in the study (76 patients receiving NEVANAC 1 mg/ml, 73 receiving ketorolac 5 mg/ml and 76 receiving placebo).

The percentage of healing on D14 was higher in the NEVANAC 1 mg/ml eye drop suspension arm (76.3%) than in the placebo arm (59.2%), $p = 0.0241$.

The only findings available for comparison with ketorolac tromethamine are for the secondary efficacy endpoints: NEVANAC 1 mg/ml was found to be not inferior to ketorolac 5 mg/ml in respect of the average inflammatory cells + erythema score on D21. The bilateral 95% confidence interval of the difference between the two treatment groups was -0.3 to 0.3 on D21. The lower limit did not exceed the predetermined non-inferiority margin of 1 unit. In addition, the percentage of healed patients on D14 was higher for NEVANAC than for ketorolac tromethamine 5 mg/ml, $p \leq 0.0319$. The percentage of patients with no eye pain was also higher in the NEVANAC arm on D3, $p \leq 0.0366$. In addition, the administration

comfort score on D7, assessed on a five-point scale, was regarded as better by patients taking NEVANAC than by those taking ketorolac 5 mg/ml, $p = 0.0158$.

Discussion

- The clinical data available does not give rise to any queries regarding the methodology.
- Efficacy was assessed on the basis of inflammation criteria for the anterior chamber of the eye, measured subjectively by a slit-lamp examination. It is not known whether administration of an anti-inflammatory eye drop simplifies surgery, reduces post-operative complications and/or shortens the time that patients need to remain in hospital or to convalesce. The secondary endpoint findings are purely exploratory.

NB: The tolerance and efficacy of NEVANAC have not been established in paediatric patients.

3.2. Adverse effects

- According to the marketing authorisation data, around 5% of patients taking part in clinical studies and receiving NEVANAC eye drops (total number in excess of 800) experienced adverse effects, which led to suspension of treatment in 0.5% of cases (the corresponding figure for patients receiving placebo was 1.3%). No serious adverse effects related to NEVANAC were reported in these studies. The adverse effects classified as common ($\geq 1/10$) were: "headache, punctate keratitis, eye pain, blurred vision, ocular pruritis, dry eye, foreign body sensation in eyes, eyelid margin crusting."
- Benzalkonium chloride (preservative) can cause inflammation and is known to discolour soft contact lenses. Punctate and/or toxic ulcerative keratopathies have been reported. Patients using these substances frequently or for prolonged periods must therefore be closely monitored.

In addition,

- Administration of a topical anti-inflammatory can lead to keratitis. Some predisposed patients can experience epithelial loss, thinning of the cornea, corneal erosion, corneal ulcer or corneal perforation following prolonged use of topical NSAIDs. These effects can cause lasting sight damage.
- Data obtained following the introduction of topical NSAIDs to the market suggests that patients undergoing complex ophthalmological procedures, corneal denervation, experiencing corneal epithelial loss, suffering from diabetes, diseases of the surface of the eye (e.g. dry eye syndrome), rheumatoid arthritis or who have numerous ophthalmological procedures within a short period may be at greater risk of corneal adverse effects that can cause lasting damage to sight. Their prolonged use can increase the frequency and severity of corneal adverse effects.

Ref.: data from the SPC.

3.3. Conclusion

The clinical assessment of NEVANAC is based on two double-blind randomised studies comparing NEVANAC (1 drop three times a day) with placebo and/or ketorolac tromethamine (5 mg/ml) in the prevention and treatment of post-operative pain and inflammation following cataract surgery. Treatment was first given on the day before surgery, and thereafter on the day of surgery and for up to 2 to 4 weeks after surgery. All patients also received antibiotic prophylaxis. Efficacy was measured subjectively by quantifying inflammatory cells in the anterior chamber by means of a slit lamp examination.

In the placebo-controlled study, the percentage of healing on D14, defined by quantification of inflammation and erythema, was higher with NEVANAC than with placebo (62.6% vs. 17.2%, $p < 0.0001$).

In the study versus placebo and active substance, the percentage of healing on D14, defined by quantification of inflammation and erythema, was higher with NEVANAC than with placebo (76.3% vs. 59.2%; $p = 0.024$) and the trial substance was not inferior to ketorolac in respect of reduction of inflammation and eye pain. Patients receiving the trial substance also experienced slightly less discomfort during administration.

The tolerance profile of NEVANAC is similar to that of other non-steroidal anti-inflammatory eye drops (used to treat punctate keratitis, eye pain, blurred vision, ocular pruritis, dry eye, foreign body sensation in eyes). The excipient (benzalkonium chloride) can lead to irritation or even ulcerative keratopathy.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Cataract is a condition in which all or part of the lens becomes opaque. The course taken varies considerably. It is usually age-related. Lens opacity and cataracts are normal consequences of ageing. Other causes include trauma and congenital disorders. Some risk factors have been identified: diabetes, severe myopia, medication (long-term corticosteroid treatment, thiazide diuretics, phenothiazines, amiodarone, isotretinoin, cytotoxic agents), ultraviolet B radiation, heavy smoking and alcoholism. Cataracts are the most common cause of blindness throughout the world. The condition causes visual handicap and impairs quality of life by restricting everyday activities such as reading and driving.

NEVANAC is used to prevent and treat the symptoms of post-operative pain and inflammation associated with cataract surgery. The efficacy/adverse effects ratio is high.

Public health benefit:

Cataract represents a moderate public health burden. Improving its management is not a need which is part of an identified public health priority.

In view of the alternative treatments available, NEVANAC is not expected to have any additional impact on morbidity and quality of life for patients undergoing cataract surgery.

The transposability of trial data is acceptable.

Consequently, NEVANAC is not expected to benefit public health.

Alternative medicinal products exist (other non-steroidal anti-inflammatory or corticosteroid eye drops).

Conclusion: the actual benefit of NEVANAC is substantial.

4.2 Improvement in actual benefit (IAB)

NEVANAC offers no improvement in actual benefit (IAB V) in the prevention and treatment of post-operative pain and inflammation related to cataract surgery compared to other NSAID eye drops.

4.3 Therapeutic use of NEVANAC⁴

Surgery involving the removal of the opaque lens and implantation of an artificial lens is the only effective treatment for cataracts. The standard technique is extracapsular extraction by means of phacoemulsification and implantation of an intraocular lens. Surgery has been shown to improve visual acuity, quality of life and the ability of patients to drive. Post-operative inflammation is a frequent complication which is prevented by administration of eye drops containing corticosteroids or non-steroidal anti-inflammatories (NSAIDs). Treatment usually starts on the day of surgery or 2 to 3 days beforehand in the case of NSAIDs, and reduced gradually over the course of 3 to 4 weeks. Corticosteroid eye drops are administered only to patients with severe inflammation as they are associated with the risks of intraocular hypertension.

⁴ Conditions for performing cataract surgery: technical setting. Assessment report produced by the Medical Treatments Assessment Department. Haute Autorité de Santé, July 2010. This report is available for download at www.has-sante.fr

Role of NEVANAC eye drops in patient management

NEVANAC is an additional alternative in the management of ocular inflammation observed immediately after cataract surgery. The clinical data available is not sufficient to distinguish NEVANAC from other non-steroidal anti-inflammatory eye drops.

4.4 Target population

Definition

The target population for NEVANAC is made up of patients undergoing cataract surgery.

Target population estimate

Over 20% of the population aged over 65 and over 60% of the population aged over 85 in France are thought to suffer from cataracts⁵. The number of hospital admissions for lens extraction in 2009 was 639,836.

The target population can be estimated on the basis of the number of cataract operations. According to data from the French healthcare information system PMSI, 643,320 cataract operations were carried out in France in 2009. N.B.: this figure is increasing every year, and the pharmaceutical firm considers that the number of cataract operations performed in 2010 could be estimated at 680,000.

In the light of this information, the target population for NEVANAC would be 650,000 to 700,000 patients at most.

4.5. Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1 Packaging: appropriate for the prescription conditions.

N.B.: The Committee regrets that a single-dose preservative-free form of NEVANAC is not available.

4.5.2 Reimbursement rate: 65%

⁵ Cataract surgery in France information sheet - health insurance - 11 September 2008.