NEVANAC 1 mg/ml, eye drops, suspension
Vial of 5 ml (CIP: 34009 383 939 3 4)

Applicant: ALCON

<table>
<thead>
<tr>
<th>INN</th>
<th>Nepafenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2011):</td>
<td>S01BC10 (anti-inflammatory agents, non-steroids)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
</tbody>
</table>
| List(s) concerned | National Health Insurance (French Social Security Code L.162-17)  
Hospital use (French Public Health Code L.5123-2) |
| Indication(s) concerned | “Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.” |

The legally binding text is the original French version
<table>
<thead>
<tr>
<th>Actual Benefit</th>
<th>Substantial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Actual Benefit</td>
<td>NEVANAC 1 mg/ ml, eye drops, suspension does not offer any improvement in actual benefit (IAB V) over standard management of postoperative macular oedema associated with cataract surgery in diabetic patients.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>NEVANAC 1 mg/ ml, eye drops, suspension is a first-line treatment in combination with a topical corticoid to reduce the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (procedure) | Initial date (centralised procedure): 11/12/2007  
Date of last revision: 22/12/2011 (extension of the indication to reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients) |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Prescribing and dispensing conditions/ special status | List I  
ATC Classification | 2011  
S: Sensory organs  
S01: Ophthalmologicals  
S01BC: Anti-inflammatory agents, non-steroids  
S01BC10: Nepafenac |

02 BACKGROUND

The indication for NEVANAC has been extended to the reduction in the risk of macular oedema associated with postoperative inflammation in cataract surgery, to a specific population of diabetic patients at risk of macular oedema.

In the former indication “Prevention and treatment of postoperative pain and inflammation associated with cataract surgery”, the Committee had taken the view that the actual benefit of this proprietary medicinal product is substantial and that it does not offer any improvement in actual benefit (IAB V) over other NSAID-based eye drops (Opinion of 15 December 2010). This previous assessment in the initial indication did not result in inclusion of NEVANAC on the list of medicines reimbursed by National Insurance and approved for hospital use. In the current request, the applicant requests only the inclusion of NEVANAC in the extension of the indication.

03 THERAPEUTIC INDICATIONS

“NEVANAC is indicated 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.”

HAS - Medical, Economic and Public Health Assessment Division 3/10
**04 DOSAGE**

“For the prevention and treatment of pain and inflammation, the dose is 1 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 up to 21 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.”

For the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients, the dose is 1 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 up to 60 days of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.”

**05 THERAPEUTIC NEED**

Postoperative inflammatory reactions are common complications of cataract surgery. Macular oedema is one of the inflammatory complications of cataract surgery. Its specific frequency is low in the absence of comorbidity, from 0 to 8.6% according to studies, but it can reach 25% when diabetes is also present.¹

Postoperative inflammatory reactions after cataract surgery are typically prevented by the instillation of eye drops containing corticoids or nonsteroidal antiinflammatory drugs (NSAIDs). Treatment is commenced on the day of the operation, or even two to three days beforehand in the case of NSAIDs, and gradually tapered over a period of three to four weeks. Corticoid eye drops, which carry a risk of intraocular hypertension, are reserved for severe inflammatory states¹,² which include macular oedema.

The results of a recent Cochrane meta-analysis³ of studies in patients with postoperative macular oedema after cataract surgery suggest that the risk of macular oedema can be reduced by local administration of a nonsteroidal antiinflammatory in combination with a corticoid. However, studies are few and far between, heterogeneous and of poor methodological quality. Additional studies are needed to confirm the usefulness of NSAID eye drops in this indication.

In diabetic patients with diabetic macular oedema (DMO), patients must be treated for this before cataract surgery can be considered, to avoid increasing the risk of postoperative macular oedema (optimal management of diabetes, treatment of concomitant hypertension, laser photocoagulation of areas of ischaemia or oedema, possible intravitreal injection of a corticoid or an anti-VEGF agent). Except for nepafenac, there are no specific data on the effect of NSAIDs in diabetic patients to reduce the risk of postoperative macular oedema associated with cataract surgery.

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**06 CLINICALLY RELEVANT COMPARATORS**

**06.1 Medicinal products**

Only the proprietary medicinal product NEVANAC has Marketing Authorisation in the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients. The proprietary medicinal product OCUFEN (flurbiprofen) has Marketing Authorisation in a similar indication “prevention of aphakic cystoid macular oedema occurring after surgical lens extraction”), but is not targeted at the population of diabetic patients and there are no specific data in this population.

In practice NEVANAC and OCUFEN, like other NSAID eye drops, are used in the prevention of postoperative inflammatory reactions, including macular oedema in diabetic patients:

- bromfenac: YELLOX 0.9 mg/ml, eye drops, solution
- diclofenac: VOLTARENE 0.1%, eye drops in single-dose container (included only on the list of medicines approved for use by hospitals) and DICLOCED 0.1%, eye drops in bottle
- indometacin: INDOCOLLYRE 0.1% in single-dose container and in bottle
- ketorolac tromethamine: ACULAR 0.5%, eye drops in bottle

These proprietary medicinal products have a substantial AB.

**06.2 Other health technologies**

Not applicable.

» **Conclusion:**
There is no relevant comparator validated by a Marketing Authorisation.

**07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT**

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSED</th>
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<tbody>
<tr>
<td></td>
<td>YES/NO</td>
</tr>
<tr>
<td></td>
<td>If not, why not</td>
</tr>
<tr>
<td>Europe</td>
<td>yes</td>
</tr>
<tr>
<td>United States</td>
<td>yes</td>
</tr>
<tr>
<td>(3 ml in a 4 ml bottle)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>yes</td>
</tr>
<tr>
<td>(5 ml in an 8 ml bottle)</td>
<td></td>
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<tr>
<td>Japan</td>
<td>yes</td>
</tr>
<tr>
<td>(5 ml bottle)</td>
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</table>
08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The assessment of the efficacy of nepafenac in the extension of its indication is based on one randomised double-blind placebo-controlled study (C-07-43) presented below.

Two other randomised double-blind comparative studies, one versus ketorolac and placebo (C-05-20), the other versus fluorometholone (C-07-32)\(^4\), have been supplied. These studies cannot be taken into consideration, as they were carried out in non-diabetic patients.

<table>
<thead>
<tr>
<th>Study C-07-43</th>
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<tr>
<td>(Singh, 2012(^5))</td>
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</table>

<table>
<thead>
<tr>
<th>Principal study objective</th>
<th>To evaluate efficacy in prevention</th>
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<tbody>
<tr>
<td>Method</td>
<td>Comparative randomised double-blind placebo-controlled study with a treatment period of 3 months.</td>
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</table>
| Population studied       | - age ≥ 18 years  
- type I or II diabetes  
- non-proliferative diabetic retinopathy  
- cataract surgery with planned intraocular lens implantation. |
| Treatment groups         | - Nepafenac 1 mg/ml (n = 126): 1 drop 3 times daily  
- Placebo (n = 127): 1 drop 3 times daily |
| Course of the study      | The treatments were administered on the day before cataract surgery, the day of the procedure and for 90 days thereafter. An additional drop was administered 30 to 120 min before the procedure.  
**Note:** The Marketing Authorisation recommends a treatment period of 2 months |
| Treatments given in combination | The patients had received prednisolone acetate 1 mg/ml ophthalmic suspension, 1 drop 4 times daily for the 2 weeks following surgery. |
| Primary endpoint         | Percentage of patients developing macular oedema in the 90 days following cataract surgery.  
Macular oedema is defined as an increase in the thickness of the central macular sub-zone of 30% or more relative to the preoperative thickness. |
| Secondary endpoint       | Percentage of patients showing a decrease in best corrected visual acuity (BCVA) score > 5 letters (ETDRS) from day 7 to day 90 (or early termination) |
| Statistical analysis     | Superiority analysis in the ITT population defined as patients exposed to the treatment who had undergone cataract surgery and had had at least one postoperative visit with an OCT examination. |

\(^4\) Miyak K et al. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. J Cataract Refract Surg 2011; 37 (9): 1581-8.  
**Results:**

A total of 263 patients underwent randomisation, 133 in the nepafenac group and 130 in the placebo group. Two hundred and fifty-one (251) patients were included in the analysis (ITT population), 125 in the nepafenac group and 126 in the placebo group.

The patients included in the ITT population had a mean age of 66.5 years, with those over 60 years accounting for 60.2% of patients. The majority (63%) were women. The patients had mild non-proliferative diabetic retinopathy in 26% of cases, moderate in 66% and severe in 8% of cases. On inclusion, the mean thickness of the central macular sub-zone was 200.8 microns. The BCVA score prior to surgery was 68.2 letters in the nepafenac group and 66.7 letters in the placebo group. Seven days after surgery the BCVA score was 81.3 letters in the nepafenac group and 80.5 letters in the placebo group.

**Primary endpoint:**
The percentage of patients developing macular oedema in the 90 days following cataract surgery was higher in the placebo group (16%) than in the nepafenac group (3.2%) (p < 0.001).

**Secondary endpoint:**
The percentage of patients showing a decrease in best corrected visual acuity (BCVA) score > 5 letters (ETDRS) from day 7 to day 90 (or early termination) was 5.6% in the nepafenac group and 11.5% in the placebo group (not significant).

**08.2 Safety/Adverse effects**

As a general rule, the most common adverse effects observed in patients undergoing cataract surgery and treated with nepafenac to prevent postoperative pain and inflammation are adverse events: keratitis, iritis, choroidal haemorrhage, corneal deposits, ocular pain, photophobia, ocular discomfort, blurred vision, dry eye, ocular discharge, allergic conjunctivitis, ocular pruritus, sensation of a foreign body in the eyes, eyelid margin crusting at, increased lacrimation, conjunctival hyperaemia.

In diabetic patients, in the prevention of postoperative macular oedema after cataract surgery, safety has been evaluated in a single study, the pivotal study C-07-43, and in a limited number of patients (n = 126) exposed to nepafenac for 90 days. Adverse effects were observed in 2% of patients and led to discontinuation of treatment in 0.8% of cases, the same level of discontinuation as in the placebo group. No serious adverse effects associated with nepafenac were reported. The most common adverse effects associated with nepafenac were punctate keratitis (2/126 or 1.6% versus 1/127 or 0.8% in the placebo group).

The SPC states that there are limited safety data in diabetic patients and that the adverse effects observed in the general population with nepafenac may occur with greater frequency in diabetic patients.

Moreover, in all patients treated with nepafenac, special attention must be paid to corneal problems. If corneal epithelial loss occurs, treatment must be stopped immediately and the condition of the cornea closely monitored. Following the market launch of NEVANAC, corneal problems of highly variable severity were reported, some sufficiently severe to require surgical intervention and/or medical treatment. In addition, more general postmarketing data on topical NSAIDs have shown there to be a risk of keratitis and corneal problems (epithelial loss, corneal thinning, erosion, ulcer or perforation) during continued use, a risk of delayed healing and an increased risk of bleeding during ophthalmological procedures. In complicated ophthalmological procedures, corneal denervation, corneal epithelial loss, diabetes mellitus, pathologies of the eye surface (e.g. dry eye syndrome), rheumatoid arthritis, or in multiple
ophthalmological procedures within a short space of time, the risk of corneal adverse effects may be increased sufficiently to jeopardize the visual prognosis. Topical NSAIDs must be used with caution in these various situations. Prolonged use of topical NSAIDs can increase the frequency and seriousness of corneal adverse effects.

The concomitant use of topical NSAIDs and topical corticoids can increase the risks associated with healing.

There are no data on the concomitant use of prostaglandin analogues and nepafenac. Given their action mechanism, the concomitant use of such substances is not recommended.

08.3 Summary & discussion

The assessment of the efficacy of nepafenac 1 mg/ml in reducing the risk of postoperative macular oedema associated with cataract surgery in diabetic patients is based on a randomised double-blind placebo-controlled study of 263 diabetic patients. The patients all had non-proliferative diabetic retinopathy, which was mild in 26% of cases, moderate in 66% and severe in 8%. The treatments were administered at a dosage of one drop three times daily on the day before cataract surgery, the day of the procedure and for 90 days thereafter (the duration of treatment validated by the Marketing Authorisation is 60 days). An additional drop was administered 30 to 120 min before the procedure. Patients additionally received a topical corticoid in combination with the study treatments.

The percentage of patients developing macular oedema in the 90 days following cataract surgery was higher in the placebo group (16%) than in the nepafenac group (3.2%) (p < 0.001).

In this study, the most common adverse effect associated with treatment was punctate keratitis, observed in two patients (one patient in the placebo group). However, the ocular adverse effects previously observed in the general population with nepafenac and familiar with topical NSAIDs are just as likely to occur in diabetic patients.

Nepafenac is the first topical NSAID with Marketing Authorisation in the prevention of macular oedema associated with cataract surgery in diabetic patients. Its efficacy has been demonstrated versus placebo in just one study in diabetic patients. However, given that in practice topical NSAIDs are routinely used in this indication in combination with a topical corticoid, it would have been desirable for this study to have had a comparator arm that included an NSAID. Moreover, it should be noted that the population specified in the Marketing Authorisation for this extension of the indication is larger than that included in the study which was targeted exclusively at patients with diabetic retinopathy.

Safety data are limited and derive solely from the pivotal study, based on 126 patients. A higher incidence of adverse effects can be expected in a larger population exhibiting a particular safety profile in diabetic patients.
09 THERAPEUTIC USE

Corticoid and NSAID eye drops are routinely used in the prevention and treatment of pain and inflammation associated with cataract surgery. NEVANAC 1 mg/ml, eye drops, suspension containing an NSAID, nepafenac, having already been granted Marketing Authorization in the prevention and treatment of pain and inflammation associated with cataract surgery, has been shown to be effective, in combination with a topical corticoid, in reducing the risk in diabetic patients of postoperative macular oedema associated with cataract surgery.

10 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

10.1 Actual benefit

- Macular oedema can be a postoperative complication associated with cataract surgery. It occurs in the weeks immediately after the procedure. In diabetic patients this postoperative risk is increased and adds to the risk of macular oedema complicating diabetic retinopathy, which leads to reduced visual acuity and can develop into blindness.

- In the extension of the indication, this proprietary medicinal product is intended as preventive treatment.

- The efficacy/adverse effects ratio is high.

- These eye drops containing nepafenac can reduce the risk of macular oedema associated with cataract surgery in diabetic patients when used in combination with a topical corticoid.

- There is no validated alternative in this indication.

- Public health benefit:
  The public health burden of cataracts is moderate. The burden represented by the population of the indication (diabetic patients) is low. Improving the management of cataracts is not a need that is an established public health priority.
  Taking into account the alternative treatments available, NEVANAC is not expected to have any additional effect on the morbidity and quality of life of diabetic patients treated with cataract surgery.
  The transferability of the study data is satisfactory.
  Consequently, NEVANAC is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of NEVANAC 1 mg/ml, eye drops, suspension is substantial in the extension of the indication to the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the extension of the indication to the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients and at the dosages in the Marketing Authorisation.

- Proposed reimbursement rate: 65%
10.2 Improvement in actual benefit (IAB)

NEVANAC 1 mg/ ml, eye drops, suspension does not offer any improvement in actual benefit (IAB V) over standard management of postoperative macular oedema associated with cataract surgery in diabetic patients.

10.3 Target population

The target population of NEVANAC is defined as the population of diabetic patients requiring cataract surgery for whom a reduction in the risk of postoperative macular oedema is necessary.

In 2011, the PMSI recorded 703,831 cataract surgery procedures in France. This number goes up each year and the figure for 2012 can be estimated at 738,000, i.e. 369,000 patients (operation on both eyes one after the other).

The proportion of diabetic patients over 65 years of age (population likely to undergo cataract surgery) is about 15%.

Consequently, applying this percentage to the number of patients undergoing cataract surgery in 2012, the annual target population of NEVANAC can be estimated at 55,350 patients.

11 Transparency Committee Recommendations

- Packaging
  Appropriate for the prescription conditions.