Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

nepafenac 1mg/mL eye drops, suspension (Nevanac®) SMC No. (813/12)

Alcon Laboratories (UK) Ltd

05 October 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

nepafenac (Nevanac®) is accepted for use within NHS Scotland.

Indication under review: reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

In the pivotal study which included diabetic patients who had undergone cataract surgery, nepafenac eye drops significantly reduced the incidence of macular oedema compared to vehicle.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Dosing Information

One drop of nepafenac 1mg/mL eye drops in the conjunctival sac of the affected eye(s) three times daily beginning one 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.

Product availability date

October 2012

Summary of evidence on comparative efficacy

Nepafenac, a non-steroidal anti-inflammatory drug (NSAID), is formulated as a suspension and administered by the topical ocular route. It is the only ocular NSAID licensed in the UK for reducing the risk of postoperative macular oedema associated with cataract surgery in diabetic patients. Macular oedema is a complication of cataract surgery, characterised by swelling within the retina due to the accumulation of excess fluid in the extracellular space of the retina. An incidence of 2% to 20% has been reported although the rate may be higher in diabetic patients, especially those with retinopathies.[1] Nepafenac is also licensed for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery. SMC issued not recommended advice for this indication in November 2009 as a result of non-submission.

One pivotal, randomised, multi-centre, double-masked vehicle-controlled parallel study (C-07-43) has been conducted in patients with type 1 or type 2 diabetes, and non-proliferative diabetic retinopathy (NPDR).[1-3] Patients of at least 18 years of age were recruited if they required cataract surgery by phacoemulsification with the implantation of a posterior chamber intraocular lens into the lens capsule. Patients were excluded if they had other conditions that may have caused macular oedema. In addition, patients were required to have a central subfield macular thickness < 250 microns (which excluded patients with pre-existing macular oedema). Patients were randomised to nepafenac eye drops 1mg/mL (one drop three times daily) or vehicle eye drops (one drop three times daily) starting on the day prior to surgery and continuing for 90 days after surgery. All patients received prednisolone acetate 1mg/mL eye drops (one drop four times daily) for two weeks post surgery, or longer if considered necessary to treat anterior segment inflammation. The intent-to-treat population comprised 125 patients in the nepafenac group and 126 patients in the vehicle group, and the number of patients who completed the study was 118 versus 102 respectively. Two-thirds of patients had moderate NPDR.

The primary endpoint was the proportion of patients who developed macular oedema (defined as an increase of 30% or more in central subfield macular thickness relative to the pre-operative baseline measurement) within 90 days following cataract surgery. The proportion of patients who developed macular oedema was significantly lower in the nepafenac group (3.2% [4/125]) than in the vehicle group (17% [21/126]) ($p<0.001$).

Secondary endpoints included the proportion of patients with a decrease of more than five letters in the best corrected visual acuity (BCVA) from day 7 to 90 (or early exit) and was 5.6% (7/125) versus 11% (14/126) (p=0.102) for nepafenac and vehicle respectively. However four patients in the nepafenac group had loss of visual acuity that was considered to be unrelated to macular oedema (n=2 posterior capsular opacification; n=1 clinically significant superficial punctate keratitis and n=1 vitreous haemorrhage) versus no patients in the vehicle group. Removal of these four patients from the analysis resulted in a significant difference between nepafenac and vehicle (2.5% versus 11%; p=0.006). Most improvements in BCVA occurred prior to day seven with small improvements in the mean BCVA for both groups from day 7 to 90 (or exit visit); the mean BCVA change (number of letters read) from day 7 to 90 (or exit visit) was 2.1 versus 0.9 (p=0.226) respectively.

The mean subfield macular thickness for nepafenac and vehicle at baseline was 197.9 microns versus 203.6 microns, and at day 90 was 206.6 microns versus 233 microns respectively. The proportion of patients with treatment failure (defined as macular oedema and/or cyst and/or changes in BCVA[3]) was significantly lower for nepafenac (28%) than for the vehicle group (47%), p=0.002. Approximately one third of patients received steroids for more than two weeks on investigator's advice. There were no significant differences in study endpoints based on a comparison of steroid dosing durations.

Summary of evidence on comparative safety

In the pivotal study, adverse events were reported in a slightly lower proportion of the nepafenac group than the vehicle group (34 [27%] and 42 [33%], respectively).[3]

The only treatment-related adverse events were two reports of punctuate keratitis and one report of corneal epithelium defect in the nepafenac group and one report of punctuate keratitis in the vehicle group. A total of 13 patients reported a serious adverse event and none were considered to be treatment related. The authors of the published pivotal study considered that 'a review of adverse events revealed no safety issues based upon assessments of incidence, seriousness, relationship to the study drug, onset, outcome, duration, severity, and patient discontinuation due to adverse events.'[1]

In the safety set submitted to the European Medicines Agency (EMA) that included three studies conducted in post cataract macular oedema (including the pivotal study described previously), adverse events were ocular in nature with the exception of one report of urticaria (in a patient treated with ketorolac). Punctate keratitis was a common adverse event (reported in ≥1% of study populations). There were no deaths in the post-cataract macular oedema studies.[2]

Summary of clinical effectiveness issues

The pivotal study compared nepafenac with vehicle in diabetic patients requiring cataract surgery. Nepafenac was significantly superior to vehicle for the primary outcome of proportion of patients with macular oedema. The results in the per protocol population were consistent with the ITT population, indicating a robust effect. However, the study had some limitations. The proportion of patients in the vehicle group who developed macular oedema (17%) was lower than that estimated by the company when designing the study (42%). The EMA considered that the absolute risk reduction of macular oedema for nepafenac relative to vehicle was limited, and judged that the use of 'prevention of' wording in the licensed indication may be misleading and therefore 'reduction in risk' wording was used. Furthermore, there was no significant difference between groups in terms of visual acuity (which is considered a clinically relevant endpoint). The study was not powered to detect a difference in this secondary endpoint but a post hoc analysis, in which four patients (whose loss of visual acuity was considered to be unrelated to macular oedema) were removed, revealed a significant difference in favour of nepafenac.

Comparative efficacy data come from the pivotal study which compared nepafenac plus prednisolone acetate drops to vehicle plus prednisolone acetate eye drops (where the steroid was administered for two weeks). Clinical experts consulted by SMC advised that the use of topical steroids is standard practice in this setting and that there is some use of NSAID eye drops to avoid macular oedema. It was noted that none of the available topical NSAIDs is licensed for the very specific indication currently under review and none has a licensed treatment duration of beyond three weeks. There are no comparative data for nepafenac versus other NSAID eye drops in this setting in a diabetic population.

In the pivotal study, treatment duration was 90 days and the majority of patients were exposed to greater than 60 days treatment with nepafenac. The EMA considered that there was no additional benefit (in macular oedema and vision function) beyond 60 days of treatment and therefore deemed the submitting company's proposal to restrict treatment duration to 60 days, to reduce the risk of corneal adverse events, was appropriate. The increased risk of corneal adverse events in certain populations, including diabetic patients with concurrent prolonged NSAID treatment, is noted in the summary of product characteristics.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing nepafenac plus the steroid prednisolone acetate versus steroid alone for the reduction in risk of postoperative macular oedema associated with cataract surgery in diabetic patients. The base case time horizon was 90 days in line with the duration of the C-07-43 clinical study.

The efficacy data used in the economic analysis was from the C-07-43 study for visual acuity outcomes at day 90. An association between visual acuity outcomes and utilities was derived from a published time-trade-off study in which general public respondents wore special contact lenses to mimic visual impairment symptoms associated with age-related macular degeneration (AMD). The utilities were assumed by the company to be appropriate for a macular oedema

population because of the similarities of central vision symptoms. The base case analysis did not assume any continuing treatment benefit in terms of visual acuity beyond 90 days.

Drug acquisition costs for nepafenac were based on a treatment duration of 60 days, with an estimated requirement of 2 bottles per treated patient. Costs were estimated for the treatment of clinically diagnosed macular oedema only, and covered drug and outpatient resource use estimated using Scottish expert clinical opinion.

Base case results were a cost per quality adjusted life year (QALY) gained of £4,181 for nepafenac plus steroid versus steroid treatment alone, based on an incremental cost of £10.49 and incremental QALY gain of 0.00251 over the 90-day time horizon. Sensitivity analysis indicated that the incremental cost-effectiveness ratio (ICER) was upwardly sensitive to the upper confidence interval for relative risk of macular oedema (£7,269 per QALY) and a lower risk of clinically diagnosed macular oedema of 3.05% (£6,668 per QALY). A scenario using an alternative source of utilities for visual acuity health states from a published study in diabetic retinopathy resulted in an ICER of £5,278 per QALY.

The main issues with the economic analysis were as follows:

- There is some uncertainty over the clinical and QALY benefit estimated for nepafenac. It appears that some element of the QALY benefit for nepafenac was associated with a reduction in sub-clinical macular oedema. However, SMC clinical experts consulted did not consider there would be a quality of life loss associated with sub-clinical macular oedema. Removing this element of QALY benefit would be expected to increase the ICER.

- The utility estimates for visual acuity are derived from a study based on symptoms associated with AMD, and it is uncertain how transferable these are to the context of post-cataract surgery in a diabetes patient population. SMC clinical experts were consulted on this issue, and their feedback indicated that they did not believe the quality of life outcomes associated with central vision symptoms in AMD were transferable to a post-cataract surgery context.

- There was no consideration in the economic analysis of whether the treated eye is the better or worse seeing eye. From experience in other areas of ophthalmology, utility benefits are usually estimated to be lower if the worse seeing eye is treated relative to treatment of the better seeing eye. If this distinction had been factored into the analysis, the ICER would have increased but is likely to have remained within acceptable limits.

Despite these limitations, the economic case was considered demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) published SIGN 116; management of diabetes in March 2010.[4] The guideline includes the following statement:

- When cataract extraction is planned in the context of advanced disease, which is not stabilised prior to surgery, the risk of progression and the need for close postoperative review should be fully discussed with the patient.

The guideline does not include advice on treatments to reduce the risk of macular oedema in diabetic patients following cataract surgery.

The Royal College of Ophthalmologists issued updated cataract surgery guidelines in September 2010.[5] The following advice is included;
If patients are at increased risk of cystoid macular oedema (CMO) (e.g. diabetes, previous CMO, previous retinal vein occlusion, epi-retinal membrane and prostaglandin use), the use of a topical non-steroidal medication before and following surgery should be considered. As yet the literature does not allow an exact regimen to be determined however.

The guidelines predate the availability of nepafenac.

Additional information: comparators

Corticosteroid and NSAID eye drops (off-label) are used.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Nepafenac 1mg/mL eye drops*	**One drop instilled in the eye three times daily for 60 days**	**30**
Bromfenac 0.9mg/mL eye drops **	One drop instilled into the eye twice daily	8.50
Ketorolac 5mg/mL eye drops**	One drop instilled into the eye three times daily	3
Prednisolone 1% eye drops	One drop instilled in the eye four times daily for two weeks	1.52

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7 August 2012 and MIMS (accessed on 29 August 2012).
*Nepafenac is used in conjunction with 2-week course of steroid (cost not included). Cost of nepafenac is based on 2 bottles.
**the use of and bromfenac and ketorolac is outwith their licensed indications and cost is for a treatment period of one month (as advised by SMC clinical experts).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 5,219 in year 1 rising to 5,859 in year 5, with an estimated uptake rate of 10% in year 1 and 30% in year 5. The gross impact on the medicines budget was estimated to be £16k in year 1 and £52k in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact remains at £16k in year 1 and £52k in year 5. SMC clinical experts have suggested that patient numbers may be lower than the company has estimated.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Singh R, Alpern L, Jaffe G.J et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clinical Ophthalmology. 2012; 6:1259-69.
2. The European Medicines Agency (EMEA) European Public Assessment Report. Nepafenac (Nevanac®). 1/02/12, EMEA/H/C/000818/II/0007/G www.ema.europa.eu
3. Alcon Resarch; A Clinical Safety and Efficacy Comparison of Nevanac® 0.1% to vehicle following cataract surgery in diabetic retinopathy patients (C-07-43). 17 December 2010.
4. Scottish Intercollegiate Guidelines Network. Management of diabetes (SIGN 116). March 2010. http://www.sign.ac.uk
5. Royal College of Ophthalmologists. Cataract surgery guidelines. September 2010. http://www.rcophth.ac.uk/

This assessment is based on data submitted by the applicant company up to and including 14 September 2012.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.