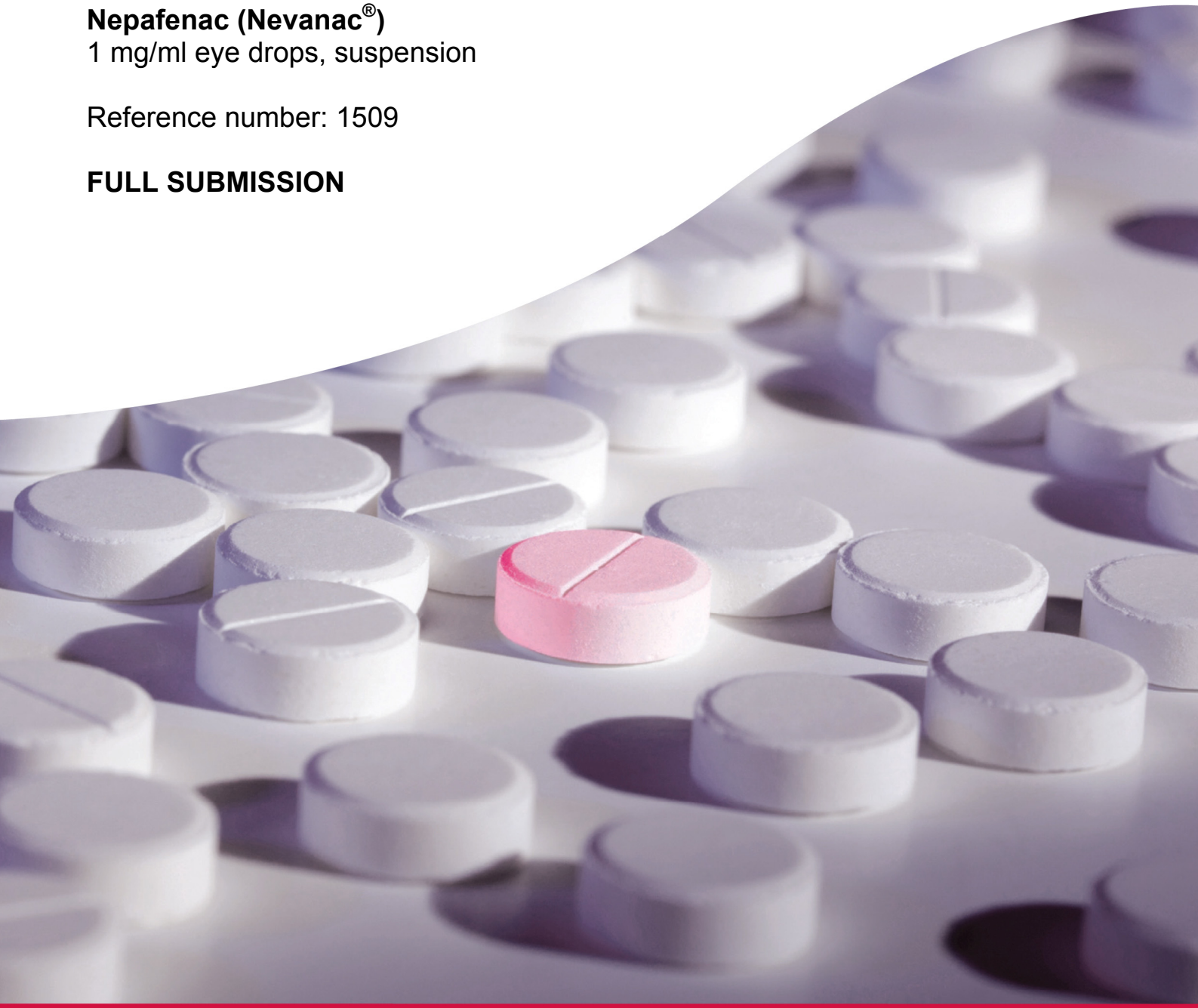
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

# AWMSG SECRETARIAT ASSESSMENT REPORT

**Nepafenac (Nevanac®)**
1 mg/ml eye drops, suspension

Reference number: 1509

**FULL SUBMISSION**



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Nepafenac (Nevanac®) 1 mg/ml eye drops, suspension. Reference number: 1509. June 2013.

# AWMSG Secretariat Assessment Report
# Nepafenac (Nevanac®) 1 mg/ml eye drops, suspension

This assessment report is based on evidence submitted by Alcon Laboratories (UK) Ltd on 20 December 2012[1].

## 1.0 PRODUCT DETAILS

| | |
|---|---|
| **Licensed indication under consideration** | Nepafenac (Nevanac®) is indicated for reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.<br><br>Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2]. |
| **Dosing** | One drop of nepafenac 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 for up to 60 days post surgery as directed. An additional drop should be administered 30 to 120 minutes prior to surgery[2]. |
| **Marketing authorisation date** | 22 December 2011 (licensed for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery on 11 December 2007)[3]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

Macular oedema is characterised by fluid accumulation within the sensory retina in the macular area, and can occur after intraocular surgery, such as cataract removal[4]. Where the fovea is involved, it results in decreased visual acuity[5]. Macular oedema is a relatively uncommon complication of cataract surgery in the general population: incidence in up to 2% of uncomplicated cases has been reported[6]. People with diabetes, however, particularly those with pre-existing diabetic retinopathy, are predisposed to cataracts and have an increased risk of developing macular oedema after cataract surgery, compared with the general population[7–9]. The average prevalence of cataract in young people with diabetes is 8%, while in older people with diabetes it is 25%[7]. Studies using optical coherence tomography (OCT) to measure macular thickness and volume identified postoperative macular oedema in 14% and 22% of diabetic patients[10,11]. The company estimates that 16% of patients undergoing cataract surgery in Wales have diabetes and are therefore at increased risk of developing postoperative macular oedema (refer to Section 5.0 for further details)[1].

Nepafenac is a nonsteroidal anti-inflammatory and analgesic prodrug, formulated as a suspension for instillation into the eye. Nepafenac penetrates the cornea, where it is converted to the nonsteroidal anti-inflammatory drug (NSAID) amfenac by ocular hydrolases and inhibits prostaglandin production[2]. It is the first medicine licensed for reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients. Other treatments used for this indication are ocular NSAIDs such as ketorolac and diclofenac, and corticosteroids such as dexamethasone and prednisolone. However, none of these medicines are licensed for the indication under consideration and are used off-label.

### 2.2 Comparators
The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were prednisolone acetate eye drops and dexamethasone eye drops.

### 2.3 Guidance and related advice
- Royal College of Ophthalmologists. Diabetic retinopathy guidelines (2012)[7].
- Royal College of Ophthalmologists. Cataract surgery guidelines (2010)[8].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guideline (CG) 87. Type 2 diabetes - newer agents (partial update of CG66) (2009)[12].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

### 3.1 Evidence submitted in support of clinical effectiveness
The company submission included evidence from two studies (C-07-43 and C-07-32) to support the efficacy and safety of nepafenac, and a third study (C-05-20) as evidence of safety only. The pivotal trial, C-07-43, compared the safety and efficacy of nepafenac plus prednisolone with placebo (vehicle) plus prednisolone. Study C-07-32 compared the preventive effect and safety of nepafenac versus fluorometholone on cystoid macular oedema after cataract extraction and intraocular lens implantation. This study was conducted in a relatively small population of Japanese patients (n = 30 in each treatment arm), excluded patients with diabetic retinopathy or uncontrolled diabetes, and compared nepafenac with a comparator outside the scope of this submission. For these reasons, efficacy results from this study will not be discussed further. Safety evidence is presented as a pooled analysis of data from C-07-43, C-07-32 and C-05-20[1].

#### 3.1.1 Study C-07-43
C-07-43 was a phase II, randomised, double-masked, vehicle-controlled trial, conducted at 41 centres in the United States[1,13]. This study was designed to evaluate the safety and efficacy of nepafenac compared to vehicle in the prevention of development of macular oedema in diabetic retinopathy patients following cataract surgery when dosed three times daily (TID) for up to 90 days. The study included type 1 or type 2 diabetic patients (aged at least 18 years) with a diagnosis of nonproliferative diabetic retinopathy that required cataract extraction (phacoemulsification with the implantation of a posterior chamber intraocular lens into the lens capsule). At least 50% of all enrolled patients were required to have moderate to severe nonproliferative diabetic retinopathy. Patients with significant corneal staining or dry eye syndrome were excluded[13]. Patients were also excluded if they had pre-existing macular oedema, or conditions (other than diabetic retinopathy) that may cause macular oedema, including pre-existing histories of retinal vein occlusions, ocular surgeries, inflammatory eye diseases, ocular infections, congenital ocular anomalies and ocular traumas[13].

Enrolled patients (n = 263) were randomised 1:1 to receive either nepafenac eye drops TID (n = 133) or vehicle TID (n = 130) in the study eye, beginning the day before cataract surgery, continuing on the day of surgery and for 90 days thereafter. All patients also received prednisolone acetate ophthalmic suspension (1 mg/ml), instilled into the study eye four times daily for two weeks after surgery (or longer if deemed necessary) to treat anterior segment inflammation[1,13]. The intent-to-treat analysis (ITT) set included all patients that were exposed to the study treatment, completed implant surgery and had at least one on-therapy postsurgical visit at which OCT was performed (n = 251; 125 in the nepafenac group and 126 in the vehicle group)[13,14].

The primary objective was to demonstrate superiority of nepafenac over vehicle, based on the proportion of patients that developed macular oedema (defined as a 30% or greater increase from pre-operative baseline measurement in central subfield macular

thickness, as measured by OCT) within 90 days following cataract surgery. Fewer patients in the nepafenac group developed macular oedema than in the vehicle group by study day 90 (4/125 [3.2%] versus 21/126 [16.7%] respectively; $p < 0.001$)[1,13]. The secondary outcome was the proportion of patients with a decrease of more than five letters in best-corrected visual acuity (BCVA) from day seven (postsurgical baseline) to day 90 (or early exit)[15]. Seven (5.6%) patients treated with nepafenac had decreases in BCVA of five or more letters at day 90 (or early exit) compared with 14 (11.5%) patients treated with vehicle ($p = 0.102$)[1,13]. Results for exploratory endpoints are summarised in Table 1, Appendix 1.

### 3.1.2 Safety evidence (pooled analysis)

Pooled safety results from C-07-43, C-07-32 and a third study, C-05-20, were submitted as evidence of safety[1]. In this analysis, 462 patients were included, of which 207 were exposed to nepafenac, 50 to ketorolac, 30 to fluorometholone and 175 to vehicle. Adverse events (AEs) reported for nepafenac were in line with its known safety profile[2] and the safety profile of other ocular NSAIDs[6]. Eye disorders were the most common classification of AE (11 events, 5.5% of total AEs)[1]. Four nepafenac-treated patients (1.9%) experienced treatment-related AEs; all were corneal adverse events[1], which are a known risk of ocular NSAID treatment[6]. No treatment-related serious AEs were reported. Three nepafenac-treated patients discontinued due to AEs: one due to keratitis, one due to punctuate keratitis and one due to vitreous haemorrhage[1].

## 3.2 AWTTC critique

- Nepafenac is the first medicine licensed for reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.
- The pivotal evidence in the company submission directly compares the efficacy and safety of nepafenac plus prednisolone versus vehicle plus prednisolone in the setting of a randomised controlled trial (C-07-43). However, it is unclear to what extent the treatment regimens used in the trial reflect clinical practice in Wales. In response to queries from AWTTC, the company confirmed that they assume patients in clinical practice would receive nepafenac in addition to prednisolone (as given in C-07-43). The duration of prednisolone therapy patients received in the trial was two weeks[1,13], but it is unclear if this reflects treatment duration in clinical practice (no recommended treatment duration is stipulated by the SPC[16]).
- No evidence comparing the clinical effectiveness of nepafenac with dexamethasone (the second comparator requested by AWTTC) has been provided. In their submission, the company state that the evidence base for the use of dexamethasone in the indication under consideration is very limited[1]. A literature search conducted by the company did not identify any suitable evidence on the clinical effectiveness of dexamethasone for the indication under consideration. Standard literature searches by AWTTC have not identified any evidence directly comparing the clinical effectiveness of nepafenac and dexamethasone within this indication.
- The results of C-07-43 demonstrated superiority of nepafenac plus prednisolone versus vehicle plus prednisolone in terms of the primary endpoint. The secondary endpoint numerically favoured nepafenac, but the difference between treatment groups did not reach statistical significance. This has been suggested to be due to confounding: in four of the seven patients in the nepafenac arm experiencing a BCVA decrease of more than five letters at day 90, BCVA loss was unrelated to macular oedema (no similar confounding reasons for BCVA losses were reported in the vehicle group)[13]. Exploratory endpoints show that statistical significance was reached for this outcome at earlier time points (see Appendix 1).

- The diagnosis of macular oedema using OCT (as in the pivotal trial) allows the detection of subclinical changes to the macula, which may not correlate with clinically relevant changes in visual function[6]. Although Royal College of Ophthalmologists guidelines state that "the level of central retinal thickness on OCT is increasingly used in treatment decisions"[7] a Cochrane Review conducted in 2011 concluded that central retinal thickness, measured with OCT, cannot be used as a stand-alone test to diagnose the central type of clinically significant macular oedema[17].
- As prolonged use of topical NSAIDs may increase the risk of occurrence and severity of corneal adverse reactions a maximum treatment duration of 60 days (where most benefit is seen) has been licensed for nepafenac, in order to minimise unnecessary patient exposure to NSAID treatment[2,6]. Although the majority of data presented in this report is for patients treated for 90 days, the Committee for Medicinal Products for Human Use (CHMP) concluded that no additional benefit seems to be obtained beyond 60 days of nepafenac treatment, in terms of either macular oedema or visual function[6].
- Patients at high risk of corneal problems were excluded from C-07-43 (the SPC states that nepafenac can be used, with caution, in such patients[2]) and ITT results excluded patients that were randomised but did not receive any dose of study treatment[13]. These factors may have caused the treatment effect to be overestimated.
- In the vehicle plus prednisolone treatment arm of C-07-43, 17% of patients developed macular oedema as defined by the primary endpoint; whereas the study design estimated that 42% of patients in this treatment arm would develop macular oedema[6]. The reasons for this discrepancy are unclear.

## 4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submission describes a cost-utility analysis of nepafenac plus prednisolone or dexamethasone compared to prednisolone or dexamethasone alone for reducing the risk of postoperative macular oedema associated with cataract surgery in diabetic patients[1].

The analysis is based on a decision analytic model. Patients enter the model upon cataract surgery and receive nepafenac plus prednisolone (or dexamethasone), or prednisolone (or dexamethasone) alone for 60 days following the procedure. Patients may or may not develop macular oedema, which is associated with visual acuity effects and impaired quality of life. Costs associated with macular oedema were assumed to be incurred only by patients with a clinical macular oedema diagnosis, defined as macular oedema with a decrease in best-corrected visual acuity of five letters or more. The base case analysis assumes a 90-day time horizon. A scenario analysis, assuming persistence of reduced visual acuity for two additional months, is also provided.

The model is populated with efficacy data from C-07-43, a randomised controlled trial comparing nepafenac plus prednisolone versus vehicle plus prednisolone in patients with diabetic retinopathy having cataract extraction (refer to Section 3.1.1 for further details). Due to a reported lack of efficacy data for dexamethasone in this patient subgroup, it was assumed that dexamethasone will demonstrate the same efficacy as prednisolone. Health utilities were estimated from logarithm of the minimum angle of resolution (logMAR) visual acuity scores for the C-07-43 study population, which have been mapped to a published time trade-off-based algorithm derived in members of the public wearing opaque contact lenses to mimic central vision loss associated with age-related macular degeneration. Resource use was informed by Welsh expert opinion.

The model assumes the same outpatient costs for the dexamethasone and prednisolone treatments. Adverse events and discontinuation of treatment were not considered.

### 4.1.2 Results

Results of the company's base case analyses are summarised in Table 1. The treatment regimen was either nepafenac one drop TID beginning one day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period, or prednisolone acetate (or dexamethasone) one drop four times daily, starting at the same treatment point and for the same duration as nepafenac.

Nepafenac treatment was more costly than prednisolone by £3.21 and dexamethasone by £1.99, and generated an additional 0.00251 quality-adjusted life-years (QALYs) (just less than one quality-adjusted day) over the 90-day time horizon. The resulting incremental cost-effectiveness ratios (ICERs) are £1,276 per QALY gained versus prednisolone and £791 per QALY gained versus dexamethasone.

**Table 1. Company-reported results of the base case analyses**

| Scenarios | Nepafenac | Comparator | ICER (£/QALY gained) | Plausible? |
|---|---|---|---|---|
| Nepafenac versus prednisolone acetate | £35.37<br>0.1563 QALYs | £32.17<br>0.1537 QALYs | £1,276 | Steroid costs excluded from nepafenac treatment?<br><br>Assumed duration of steroid treatment?<br><br>Sub-clinical macular oedema included in QALY estimates.<br><br>Analysis assumes no visual acuity effects beyond day 90 after cataract surgery. |
| Nepafenac versus dexamethasone | £35.37<br>0.1563 QALYs | £33.39<br>0.1537 QALYs | £791 | |
| ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year | | | | |

A range of one-way sensitivity analyses have been conducted by the company to address the uncertainty associated with resource use cost assumptions. The order of magnitude of the ICERs was similar within the cost range of ±20% explored and the incorporation of an assumed 10% use of off-label bevacizumab (Avastin®▼). The results of other key sensitivity and scenario analyses are summarised in Table 2. The model was most sensitive to the assumed incidence of clinically diagnosed macular oedema and relative rate of macular oedema at 90 days. The use of alternative utility values derived from another source[18] made little difference to the modelled outputs. It should be noted that all sensitivity and scenario analyses have excluded costs of steroids from nepafenac treatment, and the assumed duration of steroid treatment is uncertain.

**Table 2. Sensitivity and scenario analyses presented by the company**

| Scenarios | ICER (£/QALY gained) | Plausible? |
|---|---|---|
| **Clinically diagnosed macular oedema:**<br>3.05% (base case: 4.7%)<br><br>Nepafenac versus prednisolone<br>Nepafenac versus dexamethasone | <br><br><br>£4,571<br>£4,086 | Taken from published study |
| **Duration of visual acuity effects beyond 90 days:**<br>2 months (base case: 0)<br><br>Nepafenac versus prednisolone<br>Nepafenac versus dexamethasone | <br><br>£696<br>£431 | Assumption |
| **Relative risk of macular oedema:**<br>Nepafenac versus prednisolone<br>(base case: 0.19)<br>Lower limit: 0.068<br>Upper limit: 0.543<br><br>Nepafenac versus dexamethasone<br>(base case: 0.19)<br>Lower limit: 0.068<br>Upper limit: 0.543 | <br><br>Cost saving<br>£5,366<br><br><br>Cost saving<br>£4,881 | Based on 95% CI |
| **Use of bevacizumab:**<br>10% (base case: 0%)<br><br>Nepafenac versus prednisolone<br>Nepafenac versus dexamethasone | <br><br>£908<br>£423 | Not licensed for this indication in Wales, but used by small number of ophthalmologists, as acknowledged by the company.<br><br>Duration of treatment was assumed. |
| **Utility:**<br>Alternative source of utility data[18]<br><br>Nepafenac versus prednisolone<br>Nepafenac versus dexamethasone | <br><br>£1,611<br>£998 | Base case scenario produced marginally more favourable ICERs than this alternative source. Results of goodness-of-fit test for regression are not presented. |
| CI: confidence interval; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year | | |

### 4.1.3 AWTTC critique

Costs assumed for nepafenac exclude the costs of concomitant steroid and the assumed duration of treatment with comparator steroids appears to be uncertain (see Section 3.2 for further discussion). Utility values associated with visual acuity are derived using a mapping exercise and combine clinical and sub-clinical macular oedema, which may overestimate the benefit of nepafenac. Combined uncertainty in model parameters has not been assessed. Results of the cost-utility analyses presented in this submission are therefore subject to considerable uncertainty. Adjusting for several of the issues above, the ICER for nepafenac compared with steroid eye drops remains within the bounds of the usual thresholds for cost effectiveness, but analyses against alternative comparators are not considered.

Strengths of the economic evidence include:

- Cost-utility analysis is based on direct comparative effectiveness data.

Limitations of the economic evidence include:

- Due to the reported lack of efficacy data for dexamethasone in diabetic patients at risk of postoperative macular oedema, it was assumed that dexamethasone has the same efficacy as prednisolone. However, the company stated that none of the ophthalmologists who participated in a company-led survey in Wales are currently prescribing dexamethasone for this population group.
- Both clinical and subclinical macular oedema contribute to the overall QALY gains in all analyses, and it is unclear if this overestimates the benefits of

nepafenac (see Section 3.2 for further discussion). This approach has not been tested in sensitivity or scenario analyses.

- The model assumes that two bottles of nepafenac will be sufficient to complete up to 60 days of treatment, which does not account for spillage of eye drops during application associated with manual dexterity[19]. In C-07-43, nepafenac was administered in combination with steroid eye drops for the first two weeks, but these steroid costs have been excluded from the analysis. The duration of comparator steroid treatment is assumed to be the same as for nepafenac (up to 60 days), although the trial specified use of steroid for two weeks only unless longer treatment is required for anterior segment inflammation. Therefore, the base case costs would appear to be biased in favour of nepafenac. No sensitivity analyses have been conducted by the company to address these issues.
- NHS reference costs used in the model correspond to 2009–2010[20], while more recent costs are now available[21].
- No sensitivity analyses have been conducted to explore the effect of combined uncertainty in multiple parameter values.

### 4.2 Review of published evidence on cost-effectiveness

Standard literature searches identified one conference abstract on the cost-effectiveness of nepafenac compared to prednisolone acetate for the prevention of macular oedema following cataract surgery in diabetic patients in Scotland[22]. The analysis, based on a cost-utility model populated with data from C-07-43 trial, estimated a base case ICER for nepafenac compared to prednisolone acetate of £6,552 per QALY gained. This was a company-conducted analysis, and the outline of the methods appears similar to that used in the submission to AWTTC, but too few details are available to conduct a full critique.

## 5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

Based on NHS Wales statistics, the company estimated that the number of cataract operations performed in Wales in 2010–2011 was 16,681. Of these, 2,669 people (16%) were estimated to be diabetic patients at risk of developing macular oedema. The company assumed that the total number of cataract procedures will increase by 1,000 per year (no further details have been provided); therefore, the number of eligible patients will increase from 2,669 in year one to 3,309 in year five. According to company-sought expert opinion, no treatment is routinely used for this indication in Wales. The company anticipates market uptake for nepafenac to increase from 30% in year one to 70% in year five. Costs for nepafenac are based on those in the economic model.

#### 5.1.2 Results of company budget impact analysis

The estimated numbers of patients and the associated costs are summarised in Table 3. The total cost of treatment with nepafenac in Wales is estimated to be £23,893 in year one rising to £69,118 in year five. The saving due to avoided macular oedema is expected to increase from £18,198 in year one, rising to £52,644 in year five. The estimated net cost of treatment with nepafenac will be £5,695 in year one, rising to £16,474 in year five.

**Table 3. Company-reported costs associated with use of nepafenac for reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of eligible patients** | 2,669 | 2,829 | 2,989 | 3,149 | 3,309 |
| **Uptake** | 30% | 40% | 50% | 60% | 70% |
| **Number of treated patients** | 801 | 1,132 | 1,494 | 1,889 | 2,316 |
| **Nepafenac treatment costs** | £23,893 | £33,766 | £44,595 | £56,379 | £69,118 |
| **Cost saving due to avoided macular oedema** | -£18,198 | -£25,718 | -£33,966 | -£42,941 | -£52,644 |
| **Overall net costs** | £5,695 | £8,048 | £10,629 | £13,438 | £16,474 |

The company submission presents scenario analyses that assume prevalence of cataract in diabetes patients of 12.5% and 18% (base case 16%): the corresponding estimated overall net costs of treatment with nepafenac was £4,449 and £6,406 in year one, rising to £12,870 and £18,533 in year five, respectively.

### 5.1.3 AWTTC critique of the budget impact analysis

- Eligible patient numbers and uptake have been assumed. As the number of cataract procedures has been merged with number of patients with diabetes, the estimates of eligible patient numbers and use of nepafenac appear subject to considerable uncertainty.
- Company estimates of budgetary impact are based on the assumption that no treatment is used routinely for reducing the risk of postoperative macular oedema in diabetic patients undergoing cataract surgery in Wales; however, a survey conducted by the company among Welsh expert ophthalmologists suggested that 8/12 specialists use NSAIDs (pre- or post-operatively, or both) for the prevention of macular oedema in diabetic patients undergoing cataract surgery[23]. Company estimations of budget impact conservatively do not account for displacement of existing treatments.
- The analysis assumes two bottles of nepafenac are required per eye, and does not include concomitant steroid costs. Drug acquisition costs may therefore be underestimated.
- Collectively, company estimates of budget impact appear subject to uncertainty.

## 5.2. Comparative unit costs

Table 4 provides examples of drug acquisition costs for prophylaxis and reduction of inflammation following ocular surgery. Nepafenac is specifically licensed for reducing the risk of postoperative macular oedema associated with cataract surgery in diabetic patients[2]. Prednisolone is licensed for treatment of non-infected inflammatory conditions of the eye[16]. Ketorolac, diclofenac and bromfenac are licensed for treatment of post-operative inflammation (following cataract extraction)[24–27], and there is some evidence that they are used (off-label) in the patient population covered by this submission.

**Table 4. Examples of drug acquisition costs for prophylaxis and reduction of inflammation following ocular surgery.**

| Drug | Regimen | Cost per package |
|---|---|---|
| Nepafenac (Nevanac®)†<br>1 mg/ml eye drops | One drop TID starting 24 hours before surgery for up to 60 days | 2 × 5 ml = £29.84 |
| Prednisolone acetate (Pred Forte®)<br>1% eye drops | 1–2 drops, two to four times daily | 5 ml = £1.52 |
| Ketorolac (Acular®)*<br>0.5% eye drops | 1 drop TID starting 24 hours before surgery for up to three weeks | 5 ml = £3.00 |
| Diclofenac (Voltarol Ophtha®)*<br>0.1% eye drops | 1 drop four times daily for up to 28 days | 5 ml = £6.68 |
| Bromfenac (Yellox®)*<br>900 microgram/ml eye drops | 1 drop twice daily for two weeks starting the day after surgery | 5 ml = £8.50 |

TID: three times daily
Costs are based on Monthly Index of Medical Specialities list prices as of 5 February 2013[28].
This table does not imply therapeutic equivalence of drugs or the stated doses.
† Used in conjunction with short-term steroid eye drops: cost of steroid not included.
* Not specifically licensed for prevention or treatment of macular oedema. See relevant SPCs for full application details[24–27].

## 6.0 ADDITIONAL INFORMATION

### 6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, nepafenac (Nevanac®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that nepafenac (Nevanac®) will be supplied by a home healthcare provider.

### 6.2 Ongoing studies

The company submission highlighted one ongoing study (C-09-003) comparing nepafenac versus vehicle in adult patients with non-proliferative diabetic retinopathy, undergoing cataract extraction with implantation of a posterior chamber intra-ocular lens[1]. The timescale within which the study will report was not disclosed.

### 6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

### 6.4 Evidence search

**Date of evidence search:** 29 January and 1 February 2013.
**Date range of evidence search:** No date limits were applied to database searches.

## REFERENCES


1 Alcon Laboratories (UK) Ltd. Form B: Detailed appraisal submission. Nepafenac (Nevanac®). Dec 2012.

2 Alcon Laboratories (UK) Ltd. Nevanac® 1 mg/ml eye drops, suspension. Summary of Product Characteristics. Oct 2012. Available at: http://www.medicines.org.uk/EMC/medicine/21742. Accessed Feb 2013.

3 European Medicines Agency. Nevanac®. Procedural steps taken and scientific information after the authorisation. Oct 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000818/WC500027157.pdf. Accessed Feb 2013.

4 Tasman W, Jaeger EA. *The Wills Eye Hospital atlas of clinical opthamology.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

5 Kent D, Vinores SA, Campochiaro P. Macular oedema: the role of soluble mediators. *British Journal of Ophthalmology* 2000; 84 (5): 542-5.

6 European Medicines Agency. Assessment Report: Nevanac® (nepafenac). Procedure No.: EMEA/H/C/000818/II/0007/G. Feb 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000818/WC500122742.pdf. Accessed Feb 2013.

7 Royal College of Ophthalmologists. Diabetic retinopathy guidelines. Dec 2012. Available at: http://www.rcophth.ac.uk/core/core_picker/download.asp?id=1533&filetitle=Diabetic+Retinopathy+Guidelines+2012. Accessed Feb 2013.

8 Royal College of Ophthalmologists. Cataract surgery guidelines. Sep 2010. Available at: http://www.rcophth.ac.uk/core/core_picker/download.asp?id=544&filetitle=Cataract+Surgery+Guidelines+2010. Accessed Feb 2013.

9 Greenberg PB, Tseng VL, Wu WC et al. Prevalence and predictors of ocular complications associated with cataract surgery in United States veterans. *Ophthalmology* 2011; 118 (3): 507-14.

10 Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. *Ophthalmology* 2007; 114 (5): 881-9.

11 Torrón-Fernández-Blanco C, Ruiz-Moreno O, Ferrer-Novella E et al. Pseudophakic cytoid macular edema. Assessment with optical coherence tomography. *Arch Soc Esp Oftalmol* 2006; 81: 147-54.

12 National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (partial update of CG66). May 2009. Available at: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12165. Accessed Feb 2013.

13 Singh R, Alpern L, Jaffe GJ et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. *Clin Ophthalmol* 2012; 6: 1259-69.

14 Alcon Research Ltd. A clinical safety and efficacy comparison of Nevanac® 0.1% to vehicle following cataract surgery in diabetic retinopathy patients. Dec 2010.

15 ClinicalTrials.gov. A clinical safety and efficacy comparison of Nevanac® 0.1% to vehicle after cataract surgery in diabetic retinopathy patients. Oct 2012. Available at: http://clinicaltrials.gov/show/NCT00782717. Accessed Feb 2013.

16 Allergan Ltd. Pred Forte® 1% w/v, eye drops suspension. Summary of Product Characteristics. Jun 2010. Available at: http://www.medicines.org.uk/EMC/medicine/5289. Accessed Feb 2013.

17 Virgili G, Menchini F, Murro V et al. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev* 2011; (7): CD008081.

18 Lloyd A, Nafees B, Gavriel S et al. Health utility values associated with diabetic retinopathy. *Diabet Med* 2008; 25 (5): 618-24.
19 Hennessy AL, Katz J, Covert D et al. A video study of drop instillation in both glaucoma and retina patients with visual impairment. *Am J Ophthalmol* 2011; 152 (6): 982-8.
20 Department of Health. NHS reference costs for 2009-2010. Jan 2011. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459. Accessed Mar 2013.
21 Department of Health. NHS reference costs for 2011-2012. Jan 2012. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132390. Accessed Mar 2013.
22 Jackson D, Fisher R, Latif F. Nepafenac for the reduction in risk of post-operative macular oedema associated with cataract surgery in diabetic patients: A cost-effectiveness estimation for Scotland. *Value in Health* 2012; 15 (7): A520.
23 Alcon Laboratories (UK) Ltd. Welsh ophthalmologists - survey questions (data on file). 2012.
24 Allergan Ltd. Acular®. Summary of Product Characteristics. Oct 2011. Available at: http://www.medicines.org.uk/EMC/medicine/108. Accessed Feb 2013.
25 Spectrum Thea Pharmaceuticals Ltd. Voltarol Ophtha® (diclofenac) Multidose. Summary of Product Characteristics. Sep 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27016. Accessed Feb 2013.
26 Spectrum Thea Pharmaceuticals Ltd. Voltarol Ophtha® (diclofenac) Unit Doses. Summary of Product Characteristics. Sep 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27017. Accessed Feb 2013.
27 Bausch & Lomb UK Ltd. Yellox® 0.9 mg/ml eye drops solution. Summary of Product Characteristics. Jul 2012. Available at: www.medicines.org.uk/EMC/medicine/24628. Accessed Feb 2013.
28 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Feb 2013. Available at: http://www.mims.co.uk/. Accessed Feb 2013.

## Appendix 1. Additional clinical information

### Table 1. Results for exploratory endpoints of study C-07-43[13]

| | Nepafenac | Vehicle | p-value |
|---|---|---|---|
| **BCVA > 5 letter decrease from day 7 (n, %)** | | | |
| **ITT data set (N)** | **N = 124** | **N = 122** | |
| Day 30 | 3 (2.4) | 18 (14.8) | < 0.001 |
| Day 60 | 3 (2.4) | 16 (13.1) | 0.002 |
| Day 90 (secondary endpoint) | 7 (5.6) | 14 (11.5) | 0.102 |
| **Categorical change in BCVA from presurgical baseline to early exit (day 90) (n, %)** | | | |
| **ITT data set (N)** | **N = 125** | **N =124** | |
| Increase | | | |
| ≥ 15 letters read | 71 (56.8) | 52 (41.9) | 0.019 |
| 10–14 letters read | 19 (15.2) | 27 (21.8) | NR |
| No change | | | |
| 5–9 letters read | 16 (12.8) | 20 (16.1) | NR |
| ± 4 letters read | 17 (13.6) | 18 (14.5) | NR |
| Decrease | | | |
| 5–9 letters read | 1 (0.8) | 5 (4.0) | NR |
| 10–14 letters read | 0 (0) | 0 (0) | NR |
| ≥ 15 letters read | 1 (0.8) | 2 (1.6) | NR |
| BCVA: best-corrected visual acuity; ITT: intent-to-treat; NR: not reported. | | | |