North East Treatment Advisory Group

Ozurdex® dexamethasone ocular implant for uveitis

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Summary

- Ozurdex® is a biodegradable implant which is injected into the eye and releases dexamethasone, a steroid, over a period of up to about six months. It has been recommended by NICE for the treatment of retinal vein occlusions. It is also licensed for the treatment of posterior segment uveitis, a rare and potentially serious inflammatory eye condition.

- In the treatment of uveitis, Ozurdex® (n = 77) has been compared with sham treatment (n = 76) in a single-dose study with up to six months follow-up. Patients also received extensive use of other 'rescue' therapies. Ozurdex® was clinically superior to sham for all outcomes at all time points. Crucially, Ozurdex® was associated with clinically significant gains in visual acuity compared with sham.

- Ozurdex® was associated with a greater burden of adverse effects, many of which were transient, mild, and self-limiting. However, of greater concern is an increased incidence of cataract and raised intra-ocular pressure compared with sham.

- Ozurdex® is a costly treatment at £1,044 per dose (implant) plus administration costs, estimated at about £620. Thus the total cost for a single dose is about £1,665.

- The annual incidence or prevalence of cases of posterior segment uveitis which requires treatment is not clear. However it is a rare condition and the prevalence within NHS North East is estimated at between 75 and 250 patients. Not of all these patients would require treatment.

- It is not entirely clear where Ozurdex® would fit into current treatment pathways for posterior segment uveitis. Information from local specialists indicates that the potential patient pool would, initially at least, be relative small, perhaps not exceeding 30 patients per annum within the region.

- Other uncertainties which will impact directly to the overall cost of treatment stem from the dose interval, which is recommended at six months as a minimum, and the duration of therapy. In addition, some patients, possibly up to half, will require bilateral treatment with an attendant increase in cost. The maximum cost per patient per annum is therefore about £6,600.

Introduction

Uveitis is a group of intraocular inflammatory disorders affecting the middle layer of the eye (the uvea) which can cause significant visual impairment and may result in partial or complete loss of vision. Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or as a result of trauma to the eye. In many cases the cause remains uncertain. [1-5]

Uveitis may be classified by the anatomical location of the inflammation; anterior (iris and ciliary body); intermediate (peripheral retina and pars plana of the ciliary body); posterior (retina and choroid) and panuveitis. Uveitis can also be divided based on its aetiology into: infectious, non-infectious, and masquerade syndromes (neoplastic and drug induced). The course of uveitis may be defined as acute, recurrent or chronic. [1-5]

Posterior segment uveitis encompasses the terms intermediate and posterior uveitis previously described. It can be localised to the back of one or both eyes. It will typically manifest with 'floaters' and gradual loss of vision, occasional photophobia, but little or no discomfort or redness. Although it is not life-threatening, posterior segment uveitis is a chronic and debilitating condition with a high-risk of permanent vision loss. Uveitis can affect people of any age, but most commonly between the ages of 20 and 59 years. Uveitis is a leading cause of visual impairment with an incidence of impairment of 35% mainly attributable to posterior uveitis. Almost half of people with posterior uveitis develop visual impairment with its attendant socioeconomic impact. [2,5,6]

It is estimated that non-infectious uveitis of the posterior segment of the eye affects around 3 to 10 persons per 100,000 in the European Union. This would equate to between 1,500 and 5,000 cases per year in England. The true incidence is difficult to determine as many cases will resolve spontaneously and not present clinically. [2,6]

Non-infectious uveitis is often associated with a substantial burden of co-morbidity. Indeed, it is often the extra-ocular symptoms which are the primary focus of treatment, with uveitis considered as a secondary manifestation. The nature of the associated co-morbidities are those with a strong autoimmune component particularly the arthropathies and psoriatic dermatologies.

The mainstay of treatment of intermediate and posterior uveitis is systemic or local corticosteroids. Posterior uveitis is often unresponsive to topical administration of steroids due to inadequate therapeutic drug penetration to the back of the eye. Initial treatment is usually by periocular and occasionally intraocular steroid injection. Long-term systemic steroid therapy, although highly effective, is associated with a variety of potentially serious adverse effects and is therefore avoided. Instead immunosuppressive drugs and biological agents such as tumour necrosis factor-inhibitors are used as 'steroid sparing' treatments. However most of these treatments are not licensed for uveitis and present their own risks with respect to adverse effect profiles.[2-5,7]

Ozurdex® (Allergan Pharmaceuticals) is a biodegradable ophthalmic implant that contains dexamethasone 700 micrograms. It is available in a complete drug delivery system for intravitreal injection directly through the white (sclera) of the eye. The drug is slowly and inconsistently released over a period of six months with peak levels occurring at about two months. In June 2011 it was licensed for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. [4,8,9]

The treatment of posterior uveitis is considered to be a specialised service according to the Department of Health definitions for specialised services. [10]

The NHS North East Treatment Advisory Group was requested by the North East Retinal Group to conduct an appraisal of, and issue a recommendation for, the use of Ozurdex® within its licensed indication for uveitis.

This report will review the evidence for the efficacy, safety, cost and practical implications of using Ozurdex® for the treatment of uveitis.

Clinical evidence [2,11]

The clinical efficacy of Ozurdex® in the treatment of non-infectious posterior uveitis has been assessed in a single, phase 3, multicentre, randomised, double-masked, sham-controlled trial known as the HURON study (chronic uveitis evaluation of the intravitreal dexamethasone implant).[9] 229 adult patients with non-infectious intermediate (81%) or posterior (19%) uveitis were randomised to a single administration with Ozurdex® 700 micrograms (n = 77) or dexamethasone implant 350 micrograms (DEX350; n = 76) or a sham procedure (n = 76), and followed for up to 26 weeks. All patients were age ≥ 18 years, had a vitreous haze score ≥ 1.5 (on a scale of 0 to 4, with higher scores indicating greater visual impairment), and best-corrected visual acuity (BCVA) score of 10 to 75 letters on a standard sight chart. Treatment groups were stratified according to high or low baseline vitreous haze scores. If both eyes were eligible for the study then only the right eye was treated. Use of rescue medication was permitted under specific conditions, including topical and low-dose systemic steroids, anti-inflammatory drugs and systemic immunosuppressant therapy. Exclusion criteria included patients with a history of glaucoma, clinically significant raised intraocular pressure (IOP) in response to steroid treatment, or recent use of blood pressure medication. There were no notable between-group differences in demographic or clinical baseline characteristics; mean patient age was about 45 years, 60 to 70% were female, and 61% were white. Baseline mean vitreous haze score was 2.0 to 2.1 in all treatment groups.

The primary outcome measure was the proportion of eyes with a vitreous haze score of zero at week eight. The presence and degree of vitreous haze was measured using a standardised photographic scale ranging from zero (no inflammation) to four (optic nerve head not visible). Secondary outcome measures included the time to a vitreous haze score of zero, the proportion of patients achieving at least one unit of improvement in vitreous haze score, mean change in vitreous haze score through week 26, and improvement in BCVA. Participants were regularly evaluated throughout the study period.

At the eight-week assessment the proportion of patients with a vitreous haze score of zero was significantly greater with Ozurdex® (47%) and DEX350 (36%) than with sham (12%). Gains observed in both active treatment groups were clinically relevant and apparent from week six through to week 26. There was a significant difference between sham and both active treatment groups in the proportion of patients achieving an improvement ≥ 1 point in vitreous haze score. The response in both active treatment groups peaked at week eight and was maintained up to week 26. At each visit the proportion of patients with BCVA gain ≥ 15 letter was significantly greater in both active treatment groups compared with sham. At week eight there was a significantly greater decrease in mean central macular thickness with active treatments compared with sham (both $p < 0.01$ vs. sham) although this was no longer significant at week 26. Throughout the study the use of rescue medication was higher in sham-treated patients compared with active treatment groups.

Table 1. Summary of selected efficacy outcomes in the HURON study [2,11]

Visit	Treatment group			Difference		
	Ozurdex® (n = 77)	DEX350 (n = 76)	Sham (n = 76)	Ozurdex® vs. sham	DEX350 vs. sham	Ozurdex® vs. DEX350
Patients with vitreous haze score of zero						
Week 8	46.8%	35.5%	11.8%	34.9% p < 0.001	23.7% p < 0.001	11.2% p = 0.158
Week 26	31.2%	28.9%	14.5%	16.7% p = 0.014	14.5% p = 0.030	2.2% p = 0.764
Patients with at least one-unit improvement from baseline in vitreous haze score						
Week 8	94.8%	86.8%	44.7%	50.1% p < 0.001	42.1% p < 0.001	8.0% p = 0.088
Week 26	81.8%	71.1%	51.3%	30.5% p < 0.001	19.7% p = 0.013	10.8% p = 0.117
Patients with ≥ 15 letter gain from baseline in BCVA						
Week 8	42.9%	39.5%	6.6%	36.3% p < 0.001	32.9% p < 0.001	3.4% p = 0.671
Week 26	37.7%	27.6%	13.2%	24.5% p < 0.001	14.5% p = 0.027	10.0% p = 0.186
Patients requiring use of rescue medication						
Week 8	7.8%	5.3%	22.4%	14.6% p < 0.012	17.1% p < 0.002	2.5% p = 0.746
Week 26	22.1%	25.0%	38.2%	16.1% p < 0.030	13.2% p = 0.081	-2.9% p = 0.670

Safety [2,11]

HURON study safety outcomes are based on 225 patients who actually received treatment out of 229 patients originally randomised to a treatment group. The overall incidence and incidence of eye-related adverse events was significantly higher in active treatment groups compared with sham. The overall incidence of non-ocular systemic adverse events was low and no particular pattern was identified. The overall incidence of treatment-related ocular adverse events in the study eye was significantly higher with Ozurdex® (59%) and DEX350 (46%) compared with sham (28%; $p \leq 0.035$).

No treatment-related ocular adverse events were reported in non-study eyes. The most frequently reported ocular adverse reactions in the study eye of patients in the 26 weeks following administration of Ozurdex® were; conjunctival haemorrhage, raised IOP, ocular discomfort, cataract, ocular hypertension and eye pain. With the exception of eye pain, these adverse events were more commonly reported with Ozurdex® than with sham treatment. At each study visit less than 5% of patients in the Ozurdex® group had a severely raised IOP and less than 8% of patients had a moderately raised IOP. Throughout the study the proportion of patients requiring IOP-lowering medication was about 23%. Most cases of raised IOP were typically transient and the majority of patients managed with observation or topical medication. Less than 8% required more than one IOP-lowering medication. No patients required laser or surgical interventions to control IOP. At week 26 there were no patients with moderately or severely raised IOP.

The development and progression of cataracts is a well documented adverse effect of steroid treatment. Cataracts were present in 32% of Ozurdex® eyes, 63% of DEX350 eyes and 49% of sham eyes at baseline. During follow-up in eyes with natural lenses, cataracts were reported as adverse events in 15% of Ozurdex® patients, 12% with DEX350, and 7% with sham ($p = 0.77$). It is not clear whether this relates to progression of pre-existing cataracts or new incident cataract. One Ozurdex® and two sham patients had cataract surgery during the study.

With respect to serious adverse events in the study eye, there were four retinal detachments (two Ozurdex® and two sham), two cataracts (one DEX350 and one sham), one necrotising retinitis (DEX350), and one incident of endophthalmitis (Ozurdex®). Three patients in the Ozurdex® group discontinued due to adverse events (retinal detachment, vitreous opacities, and cerebral infarction), and none in the DEX350 or sham groups.

Adverse events observed in the HURON study are summarised in table 2.

Table 2. Selected adverse events reported > 2% participants in any treatment group [2]

	Ozurdex® (n = 76)	**DEX350** (n = 74)	**Sham** (n = 75)
Increase in intraocular pressure	19 (25.0%)	17 (23.0%)	5 (6.7%)
Treatment-related ocular adverse events in study eye			
Conjunctival haemorrhage	23 (30.3%)	13 (17.6%)	16 (21.3%)
Ocular discomfort	10 (13.2%)	3 (4.1%)	6 (8.0%)
Cataract	9 (11.8%)	6 (8.1%)	7 (9.3%)
Ocular hypertension	6 (7.9%)	7 (9.5%)	0 (0.0%)
Eye pain	11 (14.5%)	8 (10.8%)	10 (13.3%)
Conjunctival hyperaemia	5 (6.6%)	7 (9.5%)	7 (9.3%)
Conjunctival oedema	3 (3.9%)	3 (4.1%)	4 (4.0%)
Cataract subcapsular	2 (2.6%)	5 (6.8%)	4 (5.3%)
Myodesopsia (‘floaters’)	2 (2.6%)	1 (1.4%)	0 (0.0%)
Retinal detachment	7 (9.2%)	5 (6.8%)	5 (6.7%)
Nervous system disorders			
Headache	5 (6.6%)	6 (8.1%)	5 (6.7%)
Migraine	2 (2.6%)	1 (1.4%)	0 (0.0%)
Infections			
Sinusitis	3 (3.9%)	0 (0.0%)	1 (1.3%)
Nasopharyngitis	2 (2.6%)	3 (4.1%)	1 (1.3%)
Urinary tract infection	2 (2.6%)	1 (1.4%)	1 (1.3%)
Vascular disorders: Hypertension	2 (2.6%)	0 (0.0%)	3 (4.0%)

Overall, the incidence and profile of treatment-related ocular events with Ozurdex® in the HURON study were similar to those observed with the use of Ozurdex® for other indications, with the exception of a higher incidence of conjunctival haemorrhage and cataract in patients with uveitis. [2]

Cost analysis (Costs include VAT at 20% unless otherwise indicated)

A single Ozurdex® implant system, which includes the necessary administration equipment, costs £1,044. [12] The dose frequency is dependent on response to initial treatment, but is not recommended to be any more frequent than six-monthly. [8]

The recommended dose is one Ozurdex® implant via intravitreal administration to the affected eye. If both eyes are affected they should not be treated concurrently. Repeat doses are recommended after an initial positive response to treatment followed by a subsequent loss in visual acuity which, according to clinical opinion, would benefit from re-treatment. As long as visual gain is sustained, retreatment is not indicated. Where there has been no clinically meaningful benefit from treatment following initial or subsequent treatments with Ozurdex® then no further treatments are recommended. [8]

Ozurdex® would require administration in specialist facilities which are currently only available to the local NHS from NHS acute trust providers. The cost of administration is assumed to be determined by the payment-by-results tariff code BZ23Z 'vitreous retinal procedures – category 1', which costs £619 per day-case elective episode (excluding market forces factor uplift rate, typically about 2% for NHS North East acute providers). Therefore the total cost of providing a single administration of Ozurdex® is about £1,665. [13]

With the current clinical evidence it is impossible to estimate the mean number of injections per case per annum. However, assuming a minimum six-month dose interval, the maximum annual cost per eye can be assumed at about £3,330. The available clinical evidence does not permit an estimate of the permanence or duration of treatment (i.e. the number of implants required before treatment is discontinued for any reason). It is possible that some patients may require a number of repeated implants, whereas others will require fewer or even just one. The incidence of bilateral uveitis is relatively high, affecting an estimated 50% of all patients with chronic uveitis. [2] Thus, the maximum cost per patient per annum can be assumed to be £6,660 if both eyes are treated at the maximum dose frequency.

Offset costs may arise from reductions in use of other treatments. Systemic oral and local topical therapies, where used specifically for uveitis, are relatively lost cost treatments and do not provide significant offset costs. [12] Some systemic oral immunosuppressant therapy is associated with additional safety monitoring but a reduction in these aspects of therapy would also yield only minimal offset savings. More significant savings may exist where Ozurdex® is used in preference to intravitreal triamcinolone (contra-indicated use). [14] In this instance, the cost of the triamcinolone is negligible at about £2 per dose, [12] however the required patient admission would incur the same cost as for other intravitreal drug administration and is estimated at £619. [13] As the duration of triamcinolone is reported as being about three months, [7] up to four injections may be required per annum, with an associated cost of about £2,500 per eye.

Posterior segment uveitis is a relatively rare condition, and much rarer than anterior uveitis. Using Hospital Episodes Statistics inpatient data for England [15] the estimated number of admissions for posterior segment uveitis was 158. [A] The proportion estimated for NHS North East is 5%, [16] corresponding to eight admissions. This estimate is dependent on the accuracy and reliability underpinning HES data collection, which may be weak in this example. A separate HES inpatient data set indicates 3,344 admissions for 'operations on posterior segment of eye' [B] which might also include some treatment of posterior segment uveitis. [15]

The European Medicines Agency has estimated the prevalence of non-infective posterior segment uveitis at between 3 and 10 persons per 100,000. [6] This would correspond to about 75 to 250 patients within NHS North East. [16] Therefore eight admissions per annum would correspond to an admission rate of only 3 to 10%.

A report by the National (UK) Horizon Scanning Centre estimated the annual incidence of posterior and intermediate uveitis cases combined as 26 per one million population which would correspond to about 70 cases per annum within NHS North East. [5,16] This is broadly in-line with the lower estimate using the EMA data. [6]

No cost analyses of Ozurdex® in uveitis were identified.

Points to consider

Ozurdex® is a new treatment modality for posterior segment uveitis. It offers the potential to deliver a potent steroid to the required site of action, thus potentially minimising systemic adverse effects.

A limited number of drug treatments are licensed for uveitis; all are steroid treatments, mainly oral systemic treatments but also including eye drops.

Administration of Ozurdex® is a minimally invasive procedure which will impose certain constraints on patients. In addition to any local adverse effects from the treatment, patients will also be exposed to risks associated with administration such as endophthalmitis, pain, local bleeding, raised IOP, and retinal detachment.

The evidence supporting the efficacy of Ozurdex® in the treatment of non-infectious uveitis is based on a single phase 3 randomised study consisting of only a single administration of study treatment. This demonstrated superior efficacy for Ozurdex® compared with a sham 'placebo' procedure using a range of efficacy outcomes.

Efficacy appears to be independent of the underlying severity of disease.
Change in visual acuity is a clinically relevant patient-orientated outcome and this demonstrated a three-fold improvement in the proportion of patients gaining ≥ 15 letters (~ three lines) for Ozurdex® vs. sham. However, still fewer than 50% of Ozurdex® patients achieved this benefit at 26 weeks.

[A] : HES 4-character diagnosis codes beginning H30, relating to various local inflammations of the posterior segment.
[B] : HES 3-character diagnosis code C89.

A major weakness of the evidence base is that it relates to only a single administration of Ozurdex®. It is not known what proportion of patients would require a repeated dose, nor what the mean number of doses would be or the mean dose interval. In addition, it is not known whether initial efficacy is maintained with repeated doses, or whether it further improves or deteriorates (tachyphylaxis).

The study results, whilst impressive, were not obtained in isolation. Use of rescue medication was relatively high in all treatment groups. By week 26, > 20% of Ozurdex® patients had used rescue medication at some point. Use of rescue medication was much higher in sham-treated patients at all study visits and reached nearly 40% by week 26.

The exclusion of patients with a history of glaucoma, clinically significant raised IOP in response to steroid treatment, or with recent use of hypotensive medication may limit the applicability of the safety data to the targeted patient population.

The incidence of some important adverse effects, particularly cataract, is of concern. Ozurdex® patients reported roughly double the incidence of cataract as an adverse effect compared with sham patients, affecting 15% of patients. The absence of evidence relating to repeat-dosing leaves an important gap in the assessment of longer term safety.

Ozurdex® is a costly treatment although mean costs per patient per annum have been difficult to estimate. The maximum cost per eye per annum is estimated at £3,330. A large proportion of patients may require treatment in both eyes, with an attendant potential doubling of treatment costs.

Evidence for the cost-effectiveness of Ozurdex® in uveitis is limited. NICE recently issued a positive recommendation for Ozurdex® in the treatment of retinal vein occlusions, where treatment costs are similar to those for uveitis, but where absolute and incremental gains in visual acuity were considerably less than those observed in uveitis patients.

The potential number of NHS North East patients who might suitable and therefore receive treatment with Ozurdex® in any year is not known. Epidemiological evidence indicates that the number of patients will be small, perhaps as few as eight per annum, equating to about one patient per PCT per annum. The upper limit leads to an estimation of 25 patients per annum; about two per PCT.

Ozurdex® for uveitis was not recommended by the All Wales Medicines Strategy Group in November 2011 due to non-submission from the manufacturer. The Scottish Medicines Consortium has not yet made a recommendation on the use of Ozurdex® for uveitis. Due to the relatively small target patient population, it is unlikely that NICE will conduct an appraisal of Ozurdex® for uveitis.

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Author's declaration. The lead author has no relevant interests to declare. The secondary author has participated in a non-promotional educational meeting sponsored by Allergan regarding Ozurdex® although not regarding uveitis.