Lancashire & South Cumbria Medicines Management Group

NHS Midlands and Lancashire Commissioning Support Unit

New Medicine Assessment

OZURDEX (700 micrograms of dexamethasone intravitreal implant)

Ozurdex for adult patients who have visual impairment due to diabetic macular oedema (DME) who are **not pseudophakic** or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy

Recommendation: RED

Summary of supporting evidence:

Efficacy and safety of Ozurdex previously established in numerous trials eg MEAD,[1] PLACID.[2]

Dexamethasone intravitreal implant for treating diabetic macular oedema: Technology appraisal guidance [TA349] Published: 22 July 2015.[3]

There is new evidence on the use of dexamethasone intravitreal implant, so a partial review of TA349 is planned.[4] The revised guidance is expected in September 2022.[5]

In their review, NICE are considering 2 real-world studies that reported vision gain in eyes that do not have a pseudophakic lens that was similar or better than that observed in pseudophakic eyes. A further 3 studies on the use of dexamethasone intravitreal implant in treatment-naïve eyes that do not have a pseudophakic lens including an open label study that compared dexamethasone intravitreal implant with ranibizumab and aflibercept are also included in the review.[4]

The studies being reviewed by NICE are discussed below, all conclude that Intravitreal Ozurdex provides substantial long-term benefits in the treatment of diabetic macular edema in patients with pseudophakic and non pseudophakic lenses.

Details of Review

Name of medicine (generic & brand name)**:**

OZURDEX (dexamethasone).[6]

Strength(s) and form(s):

700 micrograms intravitreal implant in applicator

Dose and administration:

The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended.

For the treatment of visual impairment due to diabetic macular oedema (DME):

Patients treated with OZURDEX who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to significant risk should be considered for retreatment.

Retreatment may be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema.

There is currently no experience of the efficacy or safety of repeat administrations in DME beyond 7 implants.

BNF therapeutic class / mode of action

Ophthalmologicals, antiinflammatory agents.

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. Vascular Endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

Licensed indication(s):

OZURDEX is indicated for the treatment of adult patients with:

• visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy

• macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO)

• inflammation of the posterior segment of the eye presenting as non-infectious uveitis

Proposed use (if different from, or in addition to, licensed indication above):

DME Licensed indication but for use in adult patients who are phakic.

Course and cost:

One 700 micrograms intravitreal implant costs £870.[7]

If dose repeated every 6 months, then annual cost per patient = £1,740

Current standard of care/comparator therapies:

Ranibizumab (Lucentis) 10 mg/ml solution for injection. The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks. [8]

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with DME, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval may be extended by up to one month at a time for DME.

In the RETAIN study, the number of injections received by patients on a 'treat and extend regimen' over two years was 12.8 injections.[9]

Cost per injection = £551.[10]

Annual cost per patient on treat and extend regimen ie 6.4 injections = £3,526.40

Relevant NICE guidance:

TA349 Dexamethasone intravitreal implant for treating diabetic macular oedema Published: 22 July 2015.[3]

There is new evidence on the use of dexamethasone intravitreal implant, so a partial review of TA349 is planned.[4] The revised guidance is expected in September 2022.[5]

The manufacturer of Ozurdex has indicated that there is new evidence for the clinical and cost effectiveness of dexamethasone intravitreal implant for treating an eye that does not have a pseudophakic lens and with diabetic macular oedema that does not respond to non-corticosteroid treatment, or for which such treatment is unsuitable.

TA613 Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. Published: November 2019.[11]

Fluocinolone acetonide and dexamethasone are both corticosteroids. The population examined in TA613 is the same as the population in the proposed part-review. In TA613 the committee accepted that both laser treatment and anti-VEGFs were appropriate comparators for decision making, which could support the use of anti-VEGFs or laser treatment as a comparator in the proposed part-review.

Background and context

In the original NICE appraisal for Ozurdex (TA 349), watch-and-wait was used as the comparator for the population who do not have a pseudophakic lens and whose DMO does not respond to non-corticosteroid treatment or for whom such treatment is unsuitable.[3]

In 2019, in NICE TA613 for Iluvien (Fluocinolone acetonide intravitreal implant), the committee accepted that the treatment pathway had changed and that the appropriate comparator for eyes that do not have a pseudophakic lens and with DMO after an inadequate response to previous therapy is laser treatment and anti-VEGFs rather than watch and wait.[12]

As the use of anti VEGFs as the comparator will remove the uncertainty caused by the watch-and-wait population in the trial not reflecting general patients, the partial review of is planned TA349.[4]

The company are offering a 50% discount on the cost of any Ozurdex used in this indication pre NICE and for 90 days post NICE. Any patients receiving Ozurdex for this indication post the NICE review, if a negative decision is made, will receive each injection at the cost of £1.[13]

Summary of evidence

Summary of efficacy data in proposed use:

NICE Review of TA349 decision paper (2021)[4]

A part-review should be conducted for those eyes within the marketing authorisation that do not have a pseudophakic lens and with diabetic macular oedema (DMO) that does not respond to non-corticosteroid treatment, or for which such treatment is unsuitable, for which dexamethasone intravitreal implant is not recommended in TA349.

For those eyes with a pseudophakic lens and with DMO that does not respond to non-corticosteroid treatment, or for which such treatment is unsuitable where dexamethasone intravitreal implant is already recommended in TA349 NICE propose the guidance remains relevant and update is not needed.

In their review, NICE are considering 2 real-world studies that reported vision gain in eyes that do not have a pseudophakic lens that was similar or better than that observed in pseudophakic eyes.

A further 3 studies on the use of dexamethasone intravitreal implant in treatment-naïve eyes that do not have a pseudophakic lens including an open label study that compared dexamethasone intravitreal implant with ranibizumab and aflibercept are also included in the review.

The Reldex Study[14]

The purpose of this study was to evaluate the efficacy and safety of intravitreal implant of dexamethasone (Ozurdex) in diabetic macular oedema in real-life practice.

In this bicentric retrospective study, the authors reviewed 128 eyes of 89 patients. Main outcome measures included changes in best-corrected visual acuity, central macular thickness, time to retreatment, and incidence of adverse effects. Linear mixed-effects models were used to study changes in best-corrected visual acuity and central macular thickness over the 3-year follow-up.

The results showed that best-corrected visual acuity increased by a mean of 3.6 letters at Month 2 ($P = 0.005$), 4.2 letters at Month 12 ($P = 0.006$), 5.3 at Month 24 ($P = 0.007$), and 9.5 letters at Month 36 ($P = 0.023$). The proportion of eyes achieving at least a 15-letter improvement from baseline was 25.4% at Month 36. Central macular thickness decreased from 451 µm to 289 µm at Month 2 ($P < 0.001$), 370 µm at Month 12 ($P < 0.001$), 377 µm at Month 24 ($P = 0.004$), and 280 µm at Month 36 ($P = 0.001$). A mean of 3.6 injections were administered over the 3-year follow-up. Ten percent of eyes developed a transient increase in intraocular pressure (IOP ≥ 25 mmHg), and cataract was removed from 47% of phakic eyes.

REINFORCE Study[15]

This study assessed the real-world effectiveness, safety, and reinjection interval of dexamethasone implant in adult patients with DME. This was a phase 4, prospective, multicentre (18 U.S. sites), observational study.

Results: The study population comprised 177 patients (180 eyes; 93.8% previously treated). Baseline mean best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were 54.4 letters and 424.6 µm, respectively. Dexamethasone implant was administered as monotherapy or with other DME therapy (55%/45%). The mean reinjection interval was 5.0 months. Mean maximum BCVA change from baseline after the first three dexamethasone implants was +9.1 letters, +7.7 letters, and +7.0 letters, respectively ($P < .001$); 36.0% of eyes

achieved 15-letter or greater BCVA improvement. Mean maximum CRT change from baseline was -137.7 µm (P < .001).

Pre-planned subgroup analysis of key efficacy parameters was performed for variables including baseline lens status. 60.6% of the study eyes with documented lens status were pseudophakic and 29.4% were phakic (1.7% were aphakic and 8.3% did not have their lens status recorded).

The mean (SD) maximum change in BCVA from baseline across all DEX injections was 12.2 (13.5) letters in baseline phakic eyes versus 11.5 (11.2) letters in baseline pseudophakic eyes.

Pro Re Nata Dexamethasone Implant for Treatment-Naive Phakic Eyes with Diabetic Macular Edema: A Prospective Study[16]

This study was designed to determine the utility and safety of the intravitreal dexamethasone implant as primary therapy (pro re nata [PRN]) in phakic eyes with early treatment-naive diabetic macular oedema (DME). It was a prospective, case series whose participants were patients with diabetes mellitus whose eyes were phakic and had early treatment-naive clinically significant macular oedema.

Patients whose eyes were phakic with DME (<3 months) were included if the central subfield thickness (CST) was >300 µm and corrected distance visual acuity (CDVA) between 0.3 and 1.0 logarithm of minimum angle of resolution. A comprehensive ocular and systemic examination was performed and the implant injected PRN using a standardized technique. Patients had follow-up at least monthly for 2 years. Descriptive statistics were used to analyse categorical variables in terms of size and proportions. The repeated-measures analysis of variance test was used to determine the change in CDVA, CST, intraocular pressure, and hard exudate area over time.

The primary outcome measure was the determination of the change in CDVA at month 24 from baseline. Secondary outcome measures included determining the change in CST, median number of injections, proportion gaining 15 letters, and complications, if any.

A total of 153 patients (85 males) were included. At 2 years, mean CDVA improved from 0.62 to 0.4 logarithm of minimum angle of resolution, and median CST improved from 397 to 236 µm. The median number of injections was 1.6. Cataract developed in 3 patients with a clear lens, and 31 patients required topical antiglaucoma therapy. Proliferative disease developed in 4 patients, which was managed with panretinal photocoagulation. None of the study patients required rescue therapy.

Intravitreal dexamethasone implant Ozurdex in the treatment of diabetic macular oedema in patients not previously treated with any intravitreal drug: a prospective 12-month follow-up study[17]

This study was conducted to evaluate the mid-long-term efficacy and safety of the dexamethasone intravitreal (DEX) implant (Ozurdex) in naïve patients with diabetic macular oedema (DME).

Methods: Prospective and single-center study conducted on consecutive patients with a diagnosis of DME, who received a DEX implant and were followed up for at least 12 months. The main outcomes measurements were the mean change in best corrected visual acuity (BCVA) and in foveal thickness (FT) as compared to the baseline values.

Results: Of the 84 screened patients 50 were included in the study. The BCVA significantly improved from 52.4 (20.4) letters at baseline to 62.6 (15.6), 61.2 (18.4), 61.6 (18.6), 60.6 (19.0), and 60.6 (18.8) at 2, 4, 6, 12 months and end of follow-up period, respectively (repeated measures ANOVA and the Greenhouse-Geisser correction; p = 0.0008). At the end of the follow-up period, a gain of BCVA of ≥5, ≥10, and ≥15 letters were observed in 26 (52.0%), 18 (36.0%), and 16 (32.0%) patients, respectively. The mean FT was significantly reduced from 446.0 (139.9) µm at baseline to 327.2 (103.6) at the end of follow-up (repeated measures

ANOVA and the Greenhouse-Geisser correction; p = .0008). During the study follow-up, the patients receive a mean of 3.4 (2.9–3.9) implants. Of the 32 phakic eyes at baseline, 17 (53.1%) either developed new lens opacity or progression of an existing opacity.

INVICTUS study[18]

To compare the efficacy of intravitreal injections (IVI) of ranibizumab, aflibercept and dexamethasone implant, in the treatment of naive diabetic macular oedema (DME) during a 12-month follow-up, in real life.

Nineteen eyes treated with ranibizumab, 20 with aflibercept and 21 with dexamethasone implant were analysed from inclusion up to 12 months (M12) with intermediate analysis at M6. Best corrected visual acuity (BCVA), fundus and central retinal thickness (CRT) using spectral-domain optical coherence tomography were performed at inclusion, M3, M6 and M12.

There was no significant difference between the three treatment groups of the proportion of phakic patients at inclusion (53% in the ranibizumab group, 59% in aflibercept group and 57% in the dexamethasone implant group).

Results:

BCVA improved

- for the ranibizumab group until 67.9 letters ±13.3 SD (+5.5 letters) at M6 and 69.6 letters ±12 SD (+7.2 letters) at 12 months (p = 0.036).
- for the aflibercept group until 63.6 letters ±15.2 SD (+6.6 letters) at M6 and 67.5 letters ±12.2 SD (+8.5 letters) at 12 months (p = 0.014).
- for the dexamethasone implant group by 66.9 letters ±15.1 SD (+7.9 letters) at M6 and 68.4 letters ±11.2 SD (+9.4 letters) at 12 months (p = 0.0023).

CRT decreased

- by 124.4 µm at M6 and 99.3 µm at M12 in the ranibizumab group,
- 144.3 µm and 101.5 µm in the aflibercept group and
- 95.6 µm and 162.7 µm in the dexamethasone implant group.

Summary of safety data[6]

The most commonly-reported adverse events reported following treatment with OZURDEX are those frequently observed with ophthalmic steroid treatment or intravitreal injections (elevated IOP, cataract formation and conjunctival or vitreal haemorrhage respectively).

Less frequently reported, but more serious, adverse reactions include endophthalmitis, necrotizing retinitis, retinal detachment and retinal tear.

With the exception of headache and migraine, no systemic adverse drug reactions were identified with the use of OZURDEX.

System organ class	Frequency	Adverse reaction
Nervous system disorders	Common	Headache
	Uncommon	Migraine
Eye disorders	Very common	Intraocular pressure increased, cataract, conjunctival haemorrhage*
	Common	Ocular hypertension, cataract subcapsular, vitreous haemorrhage**, visual acuity reduced*, visual impairment/ disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema* conjunctival hyperaemia*
	Uncommon	Necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the eye*, anterior

		chamber inflammation*, anterior chamber cells/ flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*
General disorders and administration site conditions	Uncommon	Device dislocation* (migration of implant) with or without corneal oedema , complication of device insertion resulting in ocular tissue injury* (implant misplacement)

* indicates adverse reactions considered to be related to the intravitreal injection procedure (the frequency of these adverse reactions is proportional to the number of treatments given).

** in a 24-month real world observational study in the treatment of macular oedema following RVO and non-infectious uveitis affecting the posterior segment of the eye these adverse events were reported more frequently among patients who received >2 injections vs patients who received ≤2 injections; cataract formation (24.7% vs 17.7%), cataract progression (32.0% vs 13.1%), vitreous haemorrhage (6.0% vs 2.0%), and increased IOP (24.0% vs 16.6%).

Very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Safety in DME

The clinical safety of OZURDEX in patients with diabetic macular oedema was assessed in two phase 3 randomized, double-masked, sham-controlled studies. In both studies, a total of 347 patients were randomized and received OZURDEX and 350 patients received sham.

The most frequently reported adverse reactions across the entire study period in the study eye of patients who received OZURDEX were cataract and elevated IOP (see below).

In the 3 year DME clinical studies, at baseline, 87% of patients with a phakic study eye treated with OZURDEX had some degree of lens opacification/ early cataract. The incidence of all observed cataract types (i.e. cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, cataract lenticular, cataract) was 68% in OZURDEX treated patients with a phakic study eye across the 3 year studies. 59% of patients with a phakic study eye required cataract surgery by the 3 year final visit, with the majority performed in the 2nd and 3rd years.

Mean IOP in the study eye at baseline was the same in both treatment groups (15.3 mmHg). The mean increase from baseline IOP did not exceed 3.2 mmHg across all visits in the OZURDEX group with the mean IOP peaking at the 1.5 month visit post injection and returning to approximately baseline levels by month 6 following each injection. The rate and magnitude of IOP elevation following OZURDEX treatment did not increase upon repeated injection of OZURDEX.

28% of patients treated with OZURDEX had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the 3 year studies, with the majority of these patients requiring more than one medication. Peak usage (33%) occurred during the first 12 months and remained similar from year to year.

A total of 4 patients (1%) treated with OZURDEX had procedures in the study eye for the treatment of IOP elevation. One patient treated with OZURDEX required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation, 1 patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 1 patient had an iridotomy for narrow angle glaucoma and 1 patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

Strengths and limitations of the evidence:

Strengths:

- Established product with established efficacy and safety data
- Licensed in indication under review

Limitations:

- Patient numbers quite small in the newly submitted studies
- Previous negative TA in indication under review

Summary of evidence on cost effectiveness:

Price of Ozurdex implant = £870[7] (with offered 50% discount = £435).[13]

Annual cost of patient receiving 2 injections ie every 6 months = £1,740 (£870)

Annual cost of patients receiving 3 injections ie every 4 months = £2,610.

Price of Lucentis injection = £551[10]

Annual cost per patient on treat and extend regimen ie 6.4 injections = £3,526.40

Prescribing and risk management issues:

N/A

Innovation, need, equity:

Ozurdex provides an alternative treatment option for DME to those patients who do not have a pseudophakic lens, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy

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