NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- provide more information on clinical effectiveness, including the clinical trial reports, the release of the drug over the course of 180 days, the efficacy of repeat doses, data for the comparators listed in the scope, clarification of drop-outs, loss to follow-up and 'prohibited interventions' in the trials
- provide more information on cost effectiveness, including clarification of the patient population used in the model, transition probabilities, re-treatment scenarios, sources of expert opinion, calculation of health-state utility values, utility regression, the impact of monitoring, the distribution of patients by health state and how data for life years were calculated
- clarify several issues raised by the ERG about serious errors in the modelling of the involvement of the other 'fellow' eye

Licensed indication

Dexamethasone intravitreal implant (Ozurdex, Allergan) has a UK marketing authorisation for the treatment of adult patients with macular oedema following

either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Key issues for consideration

Decision problem

- The manufacturer presented evidence for the clinical and cost effectiveness of dexamethasone versus observation for four conditions associated with macular oedema: retinal vein occlusion (RVO), CRVO, BRVO with macular haemorrhage and BRVO with insufficient response to previous laser therapy.
- The manufacturer presented evidence for the clinical and cost effectiveness of dexamethasone versus observation rather than the active comparators triamcinolone acetonide, bevacizumab and grid pattern photocoagulation.
- There is uncertainty about the frequency of re-treatment (6 months as in the randomised controlled trial or at shorter intervals) and the maximum number of implants in the absence of long-term safety data.
- There is also uncertainty about whether dexamethasone should be used before laser therapy in the treatment of BRVO.

Clinical effectiveness

- The pivotal GENEVA randomised controlled trials (RCTs) reported the effectiveness of dexamethasone for a number of outcomes. The manufacturer's submission presented the primary outcome as the proportion of patients gaining at least a 15-letter improvement on the ETDRS (Early Treatment of Diabetic Retinopathy Study) chart. Other potentially useful outcomes were mean change in best corrected visual acuity (BCVA) and the proportion of patients gaining a 10-letter improvement.
- It is unclear how generalisable results from the RCT are to clinical practice in the UK, particularly in BRVO, because visual acuity spontaneously

resolves in some people and some may receive laser treatment when macular haemorrhage has resolved.

- Dexamethasone is administered with a needle that is larger than that used for other treatments such as bevacizumab.
- In the RCT 97% of patients received treatment for the eye with the poorer vision ('the worse seeing eye').

Cost effectiveness

- The model extrapolated 6-month data for dexamethasone and 3-month data for observation to provide longer-term estimates, including estimates for re-treatment.
- The model assumed that 90% of people treated would have macular oedema in the eye with the poorer vision ('the worse seeing eye').
- The model assumed up to six treatments, based on clinical opinion. However, only two treatments were included in the clinical trials.
- In the clinical trial re-treatment occurred at 6 months but in clinical practice it may occur sooner.
- The submission did not consider re-treatment of people who had a good response only.
- Health-related quality of life was based on best corrected visual acuity (BCVA) in the eye with the poorer or better vision and severe visual impairment.
- The manufacturer initially submitted analyses using day case costs.
- The manufacturer included subsequent development of macular oedema in the eye with the better vision in the model because utility is based primarily on the eye with the better vision.
- There are uncertainties surrounding the likelihood of resolution, cataract development and cataract extraction.
- There are some subgroups in which dexamethasone may be more clinically and cost effective (CRVO, all BRVO, BRVO with macular haemorrhage,

BRVO previously treated with laser therapy, and shorter duration of macular oedema).

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with macular oedema caused by RVO	People with macular oedema caused by RVO; including all RVO, CRVO, BRVO with macular haemorrhage and BRVO previously treated with laser therapy
Intervention	Dexamethasone intravitreal implant	Dexamethasone intravitreal implant
Comparator(s)	For CRVO and BRVO: triamcinolone acetonide (IVTA; 'Kenalog' formulation or equivalent) bevacizumab best supportive care (ischaemic BRVO only) For BRVO: grid pattern photocoagulation	For CRVO and BRVO: best supportive care (observation)
Outcomes	Visual acuity (the affected eye) Visual acuity (both eyes) Contrast sensitivity Adverse effects of treatment Health-related quality of life	Visual acuity (the affected eye) Adverse effects of treatment Health-related quality of life
Economic analysis	In line with reference case	In line with reference case
Subgroups to be considered	If the evidence allows, consideration will be given to the following subgroups: BRVO and CRVO, the presence or absence of ischaemia, baseline visual acuity, baseline structural damage to the central fovea, degree of perfusion at the back of the eye, duration of macular oedema (time since diagnosis)	RVO as a group as well as specific subgroups: CRVO, BRVO with macular haemorrhage and BRVO previously treated with laser therapy Additionally, duration of macular oedema (time since diagnosis) will be considered

1.2 Evidence Review Group (ERG) comments

1.2.1 Population

The ERG considered that the inclusion of subgroups of people with CRVO and people with BRVO with macular haemorrhage (who comprise 90% of people who present with BRVO and whose condition has not responded adequately to laser therapy), rather than RVO as a single group, was appropriate because laser treatment is clinically effective and cost effective in BRVO.

1.2.2 Comparators

The ERG noted that triamcinolone acetonide, bevacizumab and grid pattern photocoagulation were identified as comparators in the scope but had not been considered as comparators by the manufacturer. The ERG highlighted that there is a lot of evidence available for these comparators, particularly for the use of bevacizumab.

1.2.3 Outcomes

The ERG considered the manufacturer's argument that contrast sensitivity was not used in routine clinical practice to be reasonable.

1.3 Statements from professional/patient groups

Submissions by patient organisations and patient experts highlighted the impact of RVO on health-related quality of life. Effects included loss of sight, increased reliance on support from family members and particular difficulties associated with the considerable risk of developing problems in the other eye.

The Royal College of Ophthalmologists submitted updated guidance for the treatment of RVO. The guidance includes recommendations for the use of unlicensed treatments but indicates that their use should be guided by General Medical Council guidelines. The guidance recommends dexamethasone or ranibizumab for CRVO if no macular ischaemia is present.

If dexamethasone or ranibizumab are not clinically appropriate, the draft guidance says that other unlicensed alternatives (such as other anti-VEGF treatments) should be considered. For ischaemic CRVO, the draft guidance recommends panretinal photocoagulation, in combination with intravitreal bevacizumab and cyclodiode laser therapy or tube/shunt surgery. For non-ischaemic BRVO the guidance recommends dexamethasone implant, modified grid laser photocoagulation and ranibizumab. If dexamethasone or ranibizumab are not clinically appropriate, other 'off-label' or unlicensed alternatives (such as other anti-VEGF treatments) should be considered if no macular ischaemia is present. For ischaemic BRVO, recommendations include waiting 3 months for natural resolution, 'off-label' use of bevacizumab and panretinal photocoagulation. The Royal College of Nursing, Royal National Institute of Blind People and Macular Disease Society also noted that triamcinolone acetonide is the current 'off-label' treatment for CRVO and BRVO (including those whose condition has not responded to laser treatment).

The guideline from the Royal College of Ophthalmologists indicates that the Kenalog formulation of triamcinolone acetonide is commonly used outside its marketing authorisation in the UK, but has a contraindication for ocular use. In addition to the known risks of cataract and raised intraocular pressure seen with the Trivaris formulation (which is not available in the UK), the preservative in the Kenalog formulation may also lead to an increased risk of sterile endophthalmitis. The guideline states that there is no meta-analysis, systematic review, or good quality RCT to suggest that the visual and anatomical responses seen with Trivaris would be replicated with preparations such as Kenalog. The guideline also refers to several case series (without controls) of people with non-ischaemic CRVO receiving intravitreal bevacizumab, but states that the dosing schedule and the long-term outcomes remained unclear. Adverse effects included severe intraocular inflammation following intravitreal administration of bevacizumab. The ERG found evidence

for the efficacy of bevacizumab from randomised and uncontrolled clinical studies.

Potential benefits of dexamethasone suggested by the Royal National Institute for the Blind and the Macular Disease Society included ability to continue day-to-day activities, retain independence and avoid reliance on family and friends. In the long term, the benefit is particularly relevant if other conditions such as age-related macular degeneration develop. They also noted that two people who have received a dexamethasone intravitreal implant found it to be surprisingly quick and pain free. Dexamethasone is the only treatment licensed for CRVO and BRVO in the UK and allows earlier treatment of the condition. The Royal College of Nursing also noted that specialist services are already able to diagnose RVO and to administer and monitor intravitreal implants, but that capacity might be an issue.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission included two randomised, sham-controlled, three-arm parallel-group studies of dexamethasone intravitreal implant in people with macular oedema secondary to RVO. The studies (GENEVA 008 and GENEVA 009) were presented separately and as a pooled analysis.

Both studies had the same design, with an initial 6-month treatment period followed by a 6-month open-label extension in which all patients in both arms of the study who met the re-treatment criteria received a dexamethasone implant. All participants had macular oedema secondary to CRVO or BRVO for at least 6 weeks to 12 months prior to study entry. Participants were allocated in a 1:1:1 ratio to receive a 700-microgram dexamethasone intravitreal implant (n = 427), a sham implant (n = 426) or a 350-microgram dexamethasone implant (n = 414) (the 350-microgram dose is not considered

in this appraisal). Patients who met the relevant criteria were re-treated at 180 days. The sham group had a needleless applicator pressed against the conjunctiva actuated with a click. Investigators were masked to study treatment.

2.1.1 Measurement of best corrected visual acuity

BCVA is the most commonly cited measure of visual function and is measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. BCVA relates to a person's visual acuity with 'corrected' (that is, by wearing spectacles) vision. The ETDRS chart displays letters arranged in rows of progressively decreasing size. The ETDRS chart consists of lines each containing 5 letters, with a halving of letter sizes every third line from top to bottom. A higher score represents better visual acuity. A one-line change on the ETDRS chart corresponds to a 5-letter score change. Visual acuity is also measured using the Snellen chart. With the Snellen chart, visual acuity is represented as a fraction. If, at 20 feet (6 metres), a person can read the letters on the row marked '20', this means they have normal vision (20/20 or 6/6). If at 20 feet (6 metres), a person can read the letters on the row marked '40', this means they have visual acuity of 20/40 (6/12) or better (that is, half normal visual acuity) (see page 42 of the manufacturer's submission for details). The usual cut-off for driving is 69 letters on the ETDRS (Snellen 20/40 or 6/12). The cut-off for legal blindness is 38 letters or less on the ETDRS (Snellen 20/200 or less, 6/60 or less).

The primary outcome for the first 6 months of the trial was the proportion of patients in the intention-to-treat (ITT) population with an improvement in BCVA in the study eye of at least 15 letters from baseline. This was assessed on days 30, 60, 90 and 180. Other outcomes included time to achieve an improvement in BCVA of at least 15 letters, mean change in BCVA, categorical change in BCVA of at least 15 letters (improvement or worsening), proportion of patients with an improvement in BCVA of at least 10 letters, contrast sensitivity using the Pelli-Robson chart, the reduction in retinal

thickness (measured by optical coherence tomography) and the proportion of patients with at least a 1-grade or 5-point improvement in Visual Function Questionnaire (VFQ-25) response for general vision.

Results for all outcomes were presented for RVO, BRVO and CRVO. Results of a post-hoc subgroup analysis on the proportion of patients with an improvement in BCVA in the study eye of at least 15 letters was reported for BRVO with macular haemorrhage and BRVO with previous laser therapy. A post-hoc analysis was also conducted of the effectiveness of dexamethosone in patients with macular oedema for more than 90 days compared with early treatment in patients with macular oedema for less than 90 days. For patients who were re-treated, data from day 210 to 360 of the open-label extension were also presented as academic in confidence information.

2.1.2 Patient characteristics

In the two GENEVA studies, the mean age of participants was 64.5 years (range 31–96 years) with just over half being male (53.4%); 65.5% had BRVO and 34.4% had CRVO. Most patients (97%) presented with macular oedema secondary to RVO in their eye with the poorer vision. The duration of macular oedema was 90 days or over at baseline for most participants. Duration was less than 90 days for 16.7% and 90–179 days for 51.9% of participants. BVCA at baseline was similar between treatment and sham groups (a mean of approximately 54 letters read correctly). In general, the patient demographics and baseline characteristics of the GENEVA 008 and GENEVA 009 studies were similar. Full patient characteristics for each study are listed in table 9 of the manufacturer's submission (page 40).

2.1.3 Results

The results are presented separately for RVO, which includes CRVO, BRVO for which the manufacturer considers laser treatment to be inappropriate (BRVO with macular haemorrhage and BRVO with previous laser treatment, which make up 90% of people with BRVO) and BRVO without macular

haemorrhage (10% of people with BRVO for whom standard care is laser treatment).

Retinal vein occlusion

In the two GENEVA studies, 21.3% of the 427 patients with a dexamethasone intravitreal implant had an improvement in BCVA from baseline of at least 15 letters at day 30 compared with 7.5% of 426 patients in the sham group. This rose to 29.3% at day 60 (compared with 11.3% in the sham group) but returned to 21.8% and 21.5% at day 90 and day 180 respectively (compared with 13.1% and 17.6% in the sham group). The differences were statistically significant ($p < 0.05$) at day 30, 60 and 90 but not at day 180. The proportion of people with a 15-letter improvement in BCVA was similar in the GENEVA 008 and 009 studies. Improvement in visual acuity appears to peak at 3 months.

In the pooled and individual GENEVA studies, the cumulative response rate for time to achieve an improvement in BCVA of at least 15 letters from baseline in the study eye was statistically significant for dexamethasone intravitreal implant versus sham ($p \leq 0.001$).

The difference in mean change from baseline BCVA, the categorical change from baseline BCVA and proportion of patients with an improvement in BCVA of at least 10 letters from baseline in the study eye were statistically significantly higher for dexamethasone intravitreal implant versus sham ($p < 0.001$, $p < 0.001$ and $p < 0.010$ respectively) at days 30, 60 and 90 in the pooled and individual GENEVA studies and at day 180 in GENEVA 009 and the pooled analysis ($p \leq 0.016$, $p \leq 0.002$ and $p \leq 0.037$ respectively). See pages 56–58 of the manufacturer's submission.

The proportion of people achieving improvement in BCVA of at least 10 letters (see page 63 of the manufacturer's submission) between day 30 and day 180 ranged from 36.5% to 51.1% in the treatment group compared to 17.4% to 29.8% with sham.

Compared with the sham group, there was no statistically significant difference in contrast sensitivity between treatment groups at baseline and at day 180 in the study eye measured using the Pelli-Robson chart (see pages 64–65 of the manufacturer's submission).

Retinal thickness in the study eye, measured by optical coherence tomography and compared with baseline, was statistically significantly less in the treatment compared with sham arm at day 90 ($p<0.001$). There was no statistically significant difference at 180 days (see page 66 of the manufacturer's submission).

The proportion of patients with at least a 1-grade improvement from baseline in VFQ-25 response for general vision (measured at each follow-up visit in the ITT population) was statistically significantly higher for dexamethasone intravitreal implant versus sham ($p \leq 0.015$) at days 30, 60 and 90 in GENEVA 009 and the pooled studies and at day 180 in GENEVA 009 ($p = 0.004$). See page 67 of the manufacturer's submission.

Central retinal vein occlusion

In the pooled analysis and GENEVA 009, the proportion of patients with an improvement in BCVA from baseline of at least 15 letters was statistically significantly higher in the dexamethasone intravitreal implant group compared with the sham group at day 30 and 60 ($p < 0.001$), but not at day 90 and 180 in the pooled analysis. Differences were not statistically significant in GENEVA 008.

Branch retinal vein occlusion

In the pooled analysis, the proportion of patients with an improvement in BCVA from baseline of at least 15 letters was statistically significantly higher in the dexamethasone intravitreal implant group compared with the sham group at day 30, 60 ($p < 0.001$) and 90 ($p = 0.006$), but not at day 180. Results were similar for the individual studies, except they were not statistically significant at day 90 in GENEVA 009.

2.1.4 Subgroup analysis

The manufacturer presented a subgroup analysis of the proportion of patients with an improvement in BCVA from baseline of at least 15 letters in subgroups with BRVO and macular haemorrhage and BRVO with previous laser therapy.

Branch retinal vein occlusion with macular haemorrhage

In the pooled analysis, the proportion of patients with an improvement in BCVA from baseline of at least 15 letters was statistically significantly higher in the dexamethasone intravitreal implant group compared with the sham group at day 30, 60 and 90 ($p \leq 0.001$), but not at day 180. Results were similar for the individual studies, except they were not statistically significant at day 90 in GENEVA 009.

Branch retinal vein occlusion with previous laser therapy

In the pooled analysis, the proportion of patients with an improvement in BCVA from baseline of at least 15 letters was statistically significantly higher in the dexamethasone intravitreal implant group compared with the sham group at all time points ($p = 0.028$ at day 30, $p < 0.001$ at day 60, , $p = 0.011$ at day 90 and $p = 0.022$ at day 180). Results were similar for the GENEVA 008 at day 30 and 60, otherwise results were not statistically significant (although the subgroups were small $n < 21$).

Table 1 Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline – subgroup analysis of pooled GENEVA studies

Day	All RVO		BRVO		BRVO macular haemorrhage		CRVO		BRVO previous laser	
	Dex (n=427)	Sham (n=426)	Dex (n=291)	Sham (n=279)	Dex (n=255)	Sham (n=260)	Dex (n=136)	Sham (n=147)	Dex (n=36)	Sham (n=36)
30	21.3%	7.5%	21.3%	7.9%	22.0%	8.8%	21.3%	6.8%	22.2%	2.8%
60	29.3%	11.3%	29.6%	12.5%	31.8%	13.5%	28.7%	8.8%	27.8%	0.0%
90	21.8%	13.1%	23.7%	14.7%	25.9%	14.6%	17.6%	10.2%	27.8%	5.6%
180	21.5%	17.6%	23.0%	20.4%	23.9%	21.5%	18.4%	12.2%	25.0%	5.6%

2.1.5 Re-treated population

[redacted]

Table 2 Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline: Pooled re-treated population[a]

		Pooled GENEVA studies	
		Re-treated population	
		Dex/Dex [redacted]	Sham/Dex [redacted]
Open-label	Day 210	[redacted]	[redacted]
	Day 240	[redacted]	[redacted]
	Day 270	[redacted]	[redacted]
	Day 360	[redacted]	[redacted]

[a] Results are from table 51 of the manufacturer's submission (page 73)

2.1.6 Early versus late treatment

Individual and pooled data from the GENEVA studies demonstrated that in patients with macular oedema for more than 90 days, a statistically significantly higher proportion achieved at least a 15-letter improvement in BCVA at days 30, 60 and 90 ($p \leq 0.033$). In GENEVA 009 the proportion was also statistically significantly higher at day 180 ($p = 0.013$) for dexamethasone versus sham. Pooled data from the GENEVA studies and individual data from GENEVA 009 demonstrated that in patients with macular oedema for 90 days or less, a statistically significantly higher proportion achieved a at least a 15-letter improvement in BCVA at day 60 ($p \leq 0.015$) with dexamethasone versus sham.

2.1.7 Safety

For all RVO at 180 days, the most common adverse events were raised intraocular pressure, eye pain and ocular hypertension. Intraocular pressure was raised in 24–27% of patients treated with dexamethasone compared with 1% in the sham group. 7–8% of patients treated with dexamethasone had eye pain compared with 3–5% in the sham group. Ocular hypertension was experienced by 4% of patients in the treated group compared with 1% in the sham group. Anterior chamber cells and retinal neovascularisation were also reported. Because of the method of administration, patients did not discontinue treatment. Other reported adverse events were retinal detachment, retinal tears, and cataract. Details of adverse events in the re-treated population are on pages 104–117 of the manufacturer's submission.

2.1.8 Other evidence

The manufacturer's submission also identified a phase II dose-ranging study (DC103-06), but this was not discussed in depth. No indirect comparison was conducted by the manufacturer. A post-hoc pooled analysis of patients achieving a BCVA of 69 or more letters or 38 or fewer letters at 180 days was used in the economic model.

2.2 Evidence Review Group comments

The ERG considered the GENEVA trials to be of high quality. The ERG noted that the proportion of patients with clinical improvement and visual acuity based on the mean letter score were more useful outcomes than time to improvement. Although there was a statistically significant increase in the BCVA based on the mean letter score with the dexamethosone intravitreal implant, the ERG did not consider this to be clinically significant because most patients did not achieve a 15-letter improvement from baseline. However, a higher proportion had an improvement of at least 10 letters. The effectiveness of the dexamethosone implant appeared to peak at around 60 days.

The ERG highlighted that the trial protocol did not allow for early re-treatment and during the trial and open-label follow-on patients received only two injections of dexamethasone. The ERG noted that the main benefit from re-treatment was in patients whose condition had responded during the initial 180-day trial period. The ERG also commented that the number of treatments needed in practice is not known and that clinical opinion estimated a maximum of six. The ERG also highlighted that data on adverse events for up to six treatments were not available, nor were data available for the use of a larger needle for implantation.

The ERG stated that the main weaknesses in the evidence were lack of long-term follow-up data (particularly on the optimum number of injections) lack of data on earlier re-treatment (before 180 days), and lack of head-to-head or indirect comparisons with other treatments (including bevacizumab).

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 Methods

The manufacturer identified one published cost–utility analysis and submitted a de novo economic model. The published analysis compared the incremental cost effectiveness of laser therapy with observation for macular oedema secondary to BRVO and found an ICER of $6118.

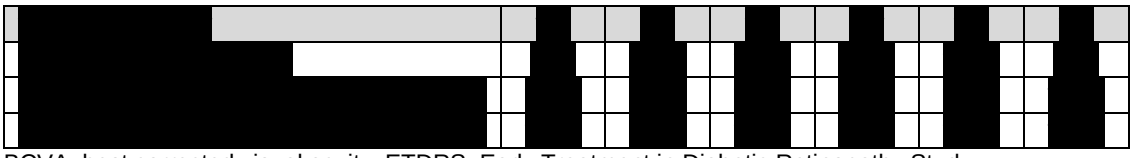
The manufacturer submitted a de novo Markov model of treatment with the dexamethosone intravitreal implant compared with sham injection in people with macular oedema and vision loss following CRVO or BRVO. Treatment was modelled over a lifetime horizon based on the transition of people between five health states based on BCVA in the affected eye and death. The patient population was based on the pooled GENEVA analysis for a modified ITT population. The model assumed 90% of people would present with

macular oedema in the eye with the poorer vision (compared with 97% in the RCTs).To capture short-term changes, the model had a cycle length of 1 month for the first 3 months following presentation with RVO, followed by a 3-month cycle in months 4–6 and 6-monthly cycles thereafter. Patients entering the model received either dexamethasone intravitreal implant or observation. Adverse events such as an increase in intraocular pressure, cataracts, retinal tears and retinal detachment were included in the model. Results were presented for the entire RVO population and the subgroups of CRVO, BRVO with macular haemorrhage, BRVO with previous laser therapy, BRVO with a diagnosis of 90 days or less at the time of treatment, and BRVO with a diagnosis of more than 90 days at the time of treatment.

For the first 6 months, transition probabilities (see pages 142–146 of the manufacturer's submission) were based on pooled patient-level data from GENEVA 008 and 009 at baseline and follow-up at 1, 2, 3 and 6 months (30, 60. 90 and 180 days) for the dexamethasone and sham groups. At 6 and 12 months data were used from patients re-treated with dexamethasone intravitreal implant in the open-label extension. Beyond 12 months data were extrapolated from the last set of data from GENEVA 008 and 009 at 6 and 12 months for treatment and re-treatment and 3 months for sham.

Health effects were assumed to last for 2.5 years in people with BRVO and 3 years in people with CRVO; and then visual acuity was assumed to be stable. Utility values were estimated using the VFQ-UI classification system and mapped onto the health states using an algorithm from a study eliciting preferences from the general population (see pages 156–157 of the manufacturer's submission). The values are presented in table 3. Health-state values were obtained using regression analyses.

Table 3 Summary of utility values for cost-effectiveness analysis estimated using VFQ-UI (commercial in confidence)[a]



BCVA, best corrected visual acuity; ETDRS, Early Treatment in Diabetic Retinopathy Study
[a]Results are from table 106 of the manufacturer's submission (page 61)

Resource use was identified from a systematic review of the literature and input from clinical specialists. Costs included drug cost and medical resource use (hospital visits, monitoring, costs associated with blindness and the cost of treating adverse events, including raised intraocular pressure, cataracts, retinal tears/detachment) (see pages 165–171 of the manufacturer's submission). The costs associated with treating adverse events were assumed to increase with the third and fourth treatment.

Key model assumptions (see table 105 of the manufacturer's submission, pages 151–154) were 90% of people treated would have macular oedema in the eye with the poorer vision, stable visual acuity for 2.5 years in people with BRVO and 3 years in people with CRVO, re-treatment at 6-monthly intervals with a maximum of five injections for BRVO and six injections for CRVO (with assumptions over the number of treatments received), extrapolation beyond the trial duration (6 months for treatment data and 3 months for sham), transition probabilities, a risk of involvement of the other eye based on 6.5% in the first year (for those with initial RVO in their eye with the poorest vision), blindness and an excess mortality hazard of 1.54 associated with a BCVA in the eye with the best vision of 38 letters or less measured by the EDTRS.

Sensitivity analyses included varying utility estimates (using an alternative method of calculating utility values which assumed lower utility in each health state for the eye with the better vision, Sharma equation), costs, stabilisation of visual acuity at day 360, extrapolation assumptions, mortality, involvement

of the other eye, discounting, re-treatment, and population characteristics (see table 115 on page 172 of the manufacturer's submission).

3.1.2 Total RVO population – base-case results

In the base case for all RVO, the total incremental cost was £1667 for dexamethasone compared with observation and the incremental QALYs were 0.23. The breakdown of these figures is presented in Tables 4 and 5. The ICER was £7368 per QALY gained for dexamethasone intravitreal implant compared with observation in all RVO (summarised in table 6).

Table 4: Life years and QALYs by health state in patients with RVO

Treated eye	Health state	Dexamethasone		Observation	
		LYs	QALYs	LYs	QALYS
Eye with the poorer vision	≤ 69	4.05	3.49	2.70	2.33
	59-68	2.65	2.25	2.38	2.02
	54-58	0.80	0.67	0.82	0.69
	44-53	1.54	1.28	1.21	1.01
	39-43	0.28	0.23	0.50	0.42
	≤ 38	1.19	0.97	2.91	2.37
Eye with the better vision	≤ 69	1.53	1.17	1.01	0.78
	59-68	1.00	0.72	0.89	0.64
	54-58	0.30	0.21	0.31	0.21
	44-53	0.58	0.38	0.45	0.30
	39-43	0.11	0.07	0.19	0.12
	≤ 38	0.40	0.24	0.98	0.58

Table 5 Costs for dexamethasone and observation – all RVO

Item	Cost dexamethasone	Cost observation	Increment	Absolute increment	Percentage increment
Drug acquisition	£2785.51	£0.00	£2785.51	£2785.51	-
Drug administration	£2074.72	£0.00	£2074.72	£2074.72	-
Routine visits and monitoring	£3725.73	£2740.29	£985.44	£985.44	36%
Adverse events	£409.49	£0.00	£409.49	£409.49	-
Vision loss: community care	£162.37	£391.62	–£229.24	£229.24	59%
Vision loss: residential care	£2901.28	£6997.48	-£4096.19	£4096.19	59%
Vision loss: depression	£78.35	£188.98	–£110.62	£110.62	59%
Vision loss: hip replacement	£107.63	£259.60	–£151.96	£151.96	59%
Total	**£12,245.09**	**£10,577.96**	**£1667.14**	**£1667.14**	**16%**

Table 6 Summary of all deterministic modelling base-case results

	All RVO	CRVO	BRVO-MH	BRVO-PL
Dexa				
Cost	**£12,245**	**£14,962**	**£10,943**	**£12,966**
QALY	**11.69**	**11.62**	**11.73**	**11.56**
observation				
Cost	**£10,578**	**£13,126**	**£9434**	**£14,184**
QALY	**11.47**	**11.32**	**11.54**	**11.24**
Net				
Cost	**£1667**	**£1836**	**£1510**	**–£1218**
QALY	**0.23**	**0.31**	**0.19**	**0.31**
ICER	**£7368**	**£6008**	**£7953**	**Dominant**

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

3.1.3 Total RVO population – sensitivity analysis

The one-way sensitivity analyses for all RVO are presented in figure 29 on page 188 of the manufacturer's submission. The factors having the largest impact on estimates of cost effectiveness were costs associated with vision loss (costs of residential care and the uptake of residential care), affected eye (proportion of people treated for macular oedema in the eye with the poorer vision) and rates of discount. When the annual cost of residential care was reduced, the ICER increased to a £20,288; all other one-way sensitivity analyses were associated with ICERs below £20,000.

The probabilistic sensitivity analysis indicated that at thresholds of £20,000 and £30,000 per QALY gained the probabilities of cost effectiveness were 81% and 93% respectively. Full sensitivity results are on pages 193 and 197 of the manufacturer's submission.

3.1.4 Subgroups results

Central retinal vein occlusion

In the base case for CRVO, the total incremental cost was £1836 and the incremental QALYs were 0.31. The cost per QALY gained was £6008 for dexamethasone compared with observation (see table 137 of the manufacturer's submission summarised in table 6).

Branch retinal vein occlusion with macular haemorrhage

In the base case for BRVO with macular haemorrhage, the total incremental cost was £1510 and the incremental QALYs were 0.19. The incremental cost per QALY gained was £7953 (see table 138 of the manufacturer's submission summarised in table 6).

Branch retinal vein occlusion with previous laser therapy

In the base case for BRVO with previous laser therapy, the total incremental cost was –£1218 (a saving) and the incremental QALYs were 0.31. Dexamethasone was dominant when compared with observation for BRVO with previous laser therapy (see table 139 of the manufacturer's submission summarised in table 6).

Branch retinal vein occlusion – duration of macular oedema

In the base case for BRVO with macular oedema for 90 days or less, the total incremental total cost over a patient's lifetime was £10,993 and the incremental QALYs were 11.75. The corresponding figures were £10,699 and 11.72 respectively for BRVO with macular oedema for more than 90 days. Dexamethasone was dominant for the group treated within 90 days and had an ICER of £11,418 per QALY gained for people treated after 90 days of diagnosis (see tables 144 and 145 of the manufacturer's submission).

3.1.5 One-way sensitivity analyses for subgroups

As for the total RVO population, the factors having the largest impact on estimates of cost effectiveness for the subgroups with CRVO, BRVO with previous laser therapy, and BRVO with macular haemorrhage were costs associated with vision loss (costs of residential care and the uptake of residential care), affected eye (proportion of people treated for macular oedema in the eye with the poorer vision), rates of discount, and assumptions

related to involvement of the other eye. The probabilistic sensitivity analysis (Table 7) indicated that at thresholds of £20,000 and £30,000 the probabilities of cost effectiveness were 81% and 93% for the CRVO subgroup, 94% and 97% for the subgroup with BRVO and previous laser therapy and 78% and 92% for the subgroup with BRVO and macular haemorrhage.

Table 7 Summary of all probabilistic modelling base-case results

		Probability of being cost effective	
	ICER	At a threshold of £20,000	At a threshold of £30,000
All RVO	£7208	81%	93%
CRVO	£6188	81%	93%
BRVO MH	£7495	78%	92%
BRVO PL	Dominant	94%	97%

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

3.1.6 Scenario analysis

The manufacturer presented a scenario analysis see tables 8 and 9 below and pages 197–200 of the manufacturer's submission.

As with all RVO, including low uptake of services for the CRVO and BRVO macular haemorrhage subgroups and applying the transition probabilities of observation patients to all dexamethasone intravitreal implant patients who are not retreated with dexamethasone intravitreal implant for the BRVO macular haemorrhage subgroup produced ICERs over £20,000. The ICER also rose to over £20,000 per QALY gained in the BRVO macular haemorrhage subgroup when the constant trial proportion retreated was changed to 78.8% of BRVO patients receiving the maximum five injections.

Table 8 Scenarios considered by the manufacturer

Scenario	Base case/default	Scenario
Source of utility estimates – eye with the better vision for all patients	VFQ-UI for both eyes	Sharma equation as source of utilities and eye with the better vision for all patients
Costs associated with vision loss – high service uptake/high cost	£8055 per year	£31,300
Costs associated with vision loss – low service uptake/low cost	£8055 per year	£1235
Stabilisation of visual acuity at day 360	Stabilisation at year 2.5 years for BRVO and 3 years for CRVO	Stabilisation at 1 year (no further dexamethasone re-treatment beyond 1 year)
Not treated – extrapolation assumptions	Not treated patients are assigned transition probabilities weighted by proportion of not treated patients resolved at day 180	All not treated patients are assigned the same transition probabilities as observation group (product matrix of day 90–180)
Excess mortality of blindness	Excess mortality of 1.54	No excess mortality
Involvement of the other eye	Probability of based on Weibull extrapolation	Risk of 2.5% per year
Discounting	3.5% for both costs and benefits	6% for costs, 1% for benefits
Numbers of patients re-treated	Absolute numbers of re-treated patients based on New York Clinical Expert Panel	Assuming 78.8% of people with BRVO receive the maximum five injections and 85.7% of people with CRVO receive the maximum six injections
All patients start with an ETDRS score of between 39 and 43 letters	Distribution at baseline is weighted average of baseline distributions for BRVO and CRVO populations of interest	All patients start model with an ETDRS score of between 39 and 43 letters
Visual decline of 1.5% every 6 months	Visual acuity is assumed to be constant from 2.5 years for BRVO and 3 years for CRVO	6-month probability of moving to next poorest health state of 1.5%
RVO in the other eye results in macular oedema in 84% of cases	RVO assumed to result in macular oedema in 100% of cases	RVO assumed to result in macular oedema in 100% of cases

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study

Table 9 Manufacturer scenario analyses

	ICER			
Scenario	All RVO	CRVO	BRVO-MH	BRVO-PL
Base case	£7368	£6008	£7953	Dominant
Stable visual acuity at day 360	£10,764	£4252	£14,283	£1028
2. Observation transition probability matrix if not treated	£24,924	£19,644	£29,045	£1,059
3. % treated as at day 180	£19,100	£11,469	£25,871	£1,392
4. Visual acuity decline	£7,685	£6,433	£8,108	Dominant

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

3.1.7 Impact of correction in the model submitted on 23 November 2010

The manufacturer corrected the model for the involvement of the other eye and submitted a revised model on 23 November 2010. Base-case deterministic modelling using this corrected model resulted in similar cost-effectiveness estimates to the original model: £6041 per QALY gained for people with CRVO, £8590 for all people with BRVO, £7987 for people with BRVO with macular haemorrhage, and dominance for dexamethasone over observation for people with BRVO and previous laser therapy.

Following the factual error check the manufacturer also provided two additional models which addressed issues raised by the ERG regarding fellow eye involvement and the units costs associated with dexamethosone treatment (papers to follow).

3.2 Evidence Review Group comments

The ERG noted that the reliability of the manufacturer's estimates of cost effectiveness in both the initial submission and the clarification response of 23 November 2010 were greatly affected by errors around the modelling of involvement of the other eye (see tables 10 and 11).

The ERG also considered that a number of the unit costs applied in the corrected model had been overestimated. For example, the cost of administering the dexamethasone intravitreal implant might have been overestimated because the implant could be given on an outpatient basis but cost were based on day case care in the manufacturer's submission. The ERG conducted a sensitivity analysis on the unit costs applied in the corrected manufacturer's model (see tables 10 and 11) and other assumptions related to the extrapolation of effectiveness data beyond the trial (table 12 and 13).

Table 10 The ERG's sensitivity analysis of the unit costs applied in the corrected model for Weibull involvement of the other eye

	ICER					
	90% of patients treated for macular oedema in eye with poorer vision			97% of patients treated for macular oedema in eye with poorer vision		
Weibull involvement of the other eye	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£6041	£7987	Dominant	£15,800	£10,206	Dominant
1. Administration cost (outpatient) £150	Dominant	£846	Dominant	£7683	£2470	Dominant
2. Annual cost of blindness £5964	£11,515	£13,067	£1445	£20,109	£15,285	£4367
3. 1&2 & cataract extraction cost of £789	£4717	£5910	Dominant	£11,966	£7531	Dominant
4. 3 & age at entry of 55	Dominant	£363	Dominant	£6026	£1522	Dominant
5. 3 & age at entry of 75	£15,923	£18,188	£5447	£25,549	£21,104	£8868

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

Table 11 The ERG's sensitivity analysis of the unit costs applied in the corrected model for no involvement of the other eye

	ICER					
	90% of patients treated for macular oedema in eye with poorer vision			97% of patients treated for macular oedema in eye with poorer vision		
No involvement of the other eye	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£17,279	£34,277	£11,905	£35,708	£47,301	£23,348
1. Administration cost (outpatient) £150	£9284	£23,553	£6212	£25,311	£34,186	£16,219
2. Annual cost of blindness £5964	£21,095	£35,979	£14,442	£37,196	£47,925	£24,301
3. 1&2 & cataract extraction cost of £789	£13,072	£25,232	£8737	£26,764	£34,782	£17,157
4. 3 & age at entry of 55	£8124	£19,379	£5390	£20,635	£27,586	£13,209
5. 3 & age at entry of 75	£24,461	£39,526	£16,565	£41,901	£52,722	£26,888

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

Table 12 Additional structural sensitivity analyses by the ERG for Weibull involvement of the other eye

	ICER					
	90% of patients treated for macular oedema in eye with poorer vision			97% of patients treated for macular oedema in eye with poorer vision		
Weibull involvement of the other eye	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£6041	£7987	Dominant	£15,800	£10,206	Dominant
Revised observation transition probability matrices	£15,395	£28,908	£1849	£28,422	£29,904	£5420
Revised transition probability matrices & costs	£11,723	£21,396	£1,366	£21,407	£22,096	£3,991

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

Table 13 Additional structural sensitivity analyses by the ERG for no involvement of the other eye

	ICER					
	90% of patients treated for macular oedema in eye with poorer vision			97% of patients treated for macular oedema in eye with poorer vision		
No involvement of the other eye	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£17,279	£34,277	£11,905	£35,708	£47,301	£23,348
Revised observation transition probability matrices	£25,163	£81,587	£19,311	£46,350	£99,018	£31,777
Revised transition probability matrices & costs	£18,981	£60,104	£14,196	£34,728	£72,831	£23,358

RVO, retinal vein occlusion; CRVO, central retinal vein occlusion; BRVO-MH, branch retinal vein occlusion with macular haemorrhage; BRVO-PL, branch retinal vein occlusion with previous laser therapy

According to the ERG, key uncertainties related to the extrapolation of data remain in the evaluation of cost effectiveness. The likely maximum number of dexamethasone administrations and frequency of re-treatment, the likelihood of resolution, the likelihood of cataract development and extraction, the likelihood of involvement of the other eye and the likelihood of the retinal vein occlusion leading to macular oedema are all important aspects of this uncertainty. In addition, the ERG questioned the way in which 6-month data from the open-label phase were used for the extrapolation of results with dexamethasone treatment and the use of 3-month data from the trial phase for extrapolation in the observation arm of the model.

According to the ERG, the evidence was also limited by no evidence examining the cost effectiveness of re-treating only those with a good response and a lack of comparisons with unlicensed comparators (when RCT and non-RCT evidence was available and could have been used in an indirect comparison).

3.3 Equalities issues

During draft scope consultation, consultees recognised that, although the prevalence of macular oedema is higher in people over 50, this was not classed an equalities issue because it does not affect equality of access to treatment.

4 Innovation

During draft consultation consultees noted that this technology is one of the first pharmacological agents licensed for the treatment of macular oedema secondary to BRVO and CRVO. Consultees also noted that this technology is potentially innovative because it involves a new drug delivery system.

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Aberdeen Health Technology Assessment Group:

- Shyangdan D, Cummins E, Lois N, et al. Dexamethasone implants in the treatment of macular oedema due to retinal vein occlusion: a single technology appraisal. November 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Allergan

II Professional/specialist, patient/carer and other groups:

- Royal College of Ophthalmologists
- Royal National Institute for Blind People – Macular Disease Society
- Royal College of Nursing