6.02 DEXAMETHASONE, intravitreal injection 700 micrograms, Ozurdex®, Allergan Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested an Authority Required listing for dexamethasone posterior segment drug delivery system 700 µg (referred to in the submission as dexamethasone implant) for the treatment of macular oedema secondary to central or branch retinal vein occlusion.

1.2 The submission included a copy of correspondence with the MSAC secretariat suggesting a coordinated submission to MSAC would be made by the sponsor for the subsidy of optical coherence tomography (OCT) for the purposes of confirming eligibility for treatment with dexamethasone implant. It was proposed to amend MBS item 11219 to accommodate the following population: central or branch retinal vein occlusion for access to initial treatment with dexamethasone in patients who are contraindicated or unsuitable for ranibizumab and aflibercept. This amendment does not include patients who have failed treatment with VEGF inhibitors; the correspondence assumed that an OCT conducted on patients for VEGF inhibitor eligibility will have already been done, and thus an additional OCT will not be necessary.

1.3 Listing was requested on the basis of a cost analysis over 3, 6, 12, or 36 months compared to vascular endothelial growth factor (VEGF) inhibitors.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with macular oedema secondary to either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) where patients are contraindicated to, unsuitable for or have failed prior treatment with VEGF inhibitors.
Intervention	Dexamethasone intravitreal implant (700 µg)
Comparator	Sham injection (as a proxy for no active treatment such as a patient managed by observation when VEGF inhibitors are contraindicated, have failed, or are otherwise unsuitable) VEGF inhibitors (ranibizumab and aflibercept) in patients who could use a VEGF inhibitor but in whom such treatment is not preferred (for example, due to patient preference or logistical reasons relating to the frequency of VEGF inhibitor injections)
Outcomes	Improvement in best corrected visual acuity (BCVA) in the affected eye Proportion of eyes with ≥10 and ≥15 letter gains in BCVA in the affected eye Reduction of macular oedema (assessed by central retinal thickness) Quality of life (Visual Function Questionnaire-25) Adverse events
Clinical claim	Dexamethasone implant is superior in terms of effectiveness and inferior in terms of safety compared to placebo when used in the treatment of retinal vein occlusion. Dexamethasone implant is inferior in terms of both effectiveness and safety compared to VEGF inhibitors when used in the treatment of retinal vein occlusion.

Source: Table 1.1.1, p.4 of the submission.
Abbreviations: VEGF, vascular endothelial growth factor

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
DEXAMETHASONE INTRAVITREAL IMPLANT, 700 microgram	1	1	$1,354.79 (published price) $[redacted] (effective price)	Ozurdex®	Allergan

PBS indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	*Patient m*ust be treated by an ophthalmologist *or in consultation with an ophthalmologist.*
Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to branched retinal vein occlusion (BRVO), **AND** Patient must have documented visual impairment defined as a best-corrected visual acuity score between 73 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/400), in the eye proposed for treatment, **AND** The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, **AND** Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; OR Patient must be unsuitable for treatment with VEGF inhibitors; OR Patient must have failed prior treatment with VEGF inhibitors, **AND**

	The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. A written application must include: • a completed authority prescription form; • a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form; and • a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	Note: No increase in the maximum quantity or number of units may be authorised. Note: No increase in the maximum number of repeats may be authorised.

PBS indication:	Central retinal vein occlusion with macular oedema
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	*Patient m*ust be treated by an ophthalmologist *or in consultation with an ophthalmologist.* .
Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), **AND** Patient must have documented visual impairment defined as a best-corrected visual acuity score between 73 and 24 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/320), in the eye proposed for treatment, **AND** The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, **AND** Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; OR Patient must be unsuitable for treatment with VEGF inhibitors; OR Patient must have failed prior treatment with VEGF inhibitors, **AND** The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. A written application must include: • a completed authority prescription form; • a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form; and • a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	Note: No increase in the maximum quantity or number of units may be authorised. Note: No increase in the maximum number of repeats may be authorised.

2.1 The submission proposed a special pricing arrangement, with an effective dispensed price for maximum quantity (DPMQ) of $[redacted] based on a [redacted]% rebate on government expenditure and a published DPMQ of $1,354.79.

2.2 The requested listing was narrower than the registered TGA indication (macular oedema secondary to branch retinal vein occlusion or central retinal vein occlusion), as it restricted use to a subgroup of patients contraindicated to, unsuitable for, or who have failed VEGF inhibitors. It was also more detailed insofar as it included definitions of visual impairment.

2.3 The submission did not explicitly define patients who would be contraindicated to VEGF inhibitors, or provide definitions of prior treatment failure. No direct comparative clinical evidence was provided for this population. The wording of the restriction was ambiguous as it was unclear whether patients had to have failed/be contraindicated to/unsuitable for one or both VEGF inhibitors. The Pre-Sub Committee Response (PSCR) (p4) argued that the PBS restriction relating to the use of dexamethasone implant in diabetic macular oedema (DMO) in an equivalent population does not provide a definition.

2.4 The ESC noted that the proposed listings for retinal vein occlusion (RVO) were modelled on the current PBS listing for dexamethasone in DMO, which positions dexamethasone as second line therapy after VEGF inhibitors (ranibizumab and aflibercept). However, this raised the following issues for each RVO subgroup requested:

- Contraindicated to VEGF inhibitors (nominated comparator: placebo): treatment with VEGF inhibitors is contraindicated in patients with pre-existing hypersensitivity. The ESC considered that it is unclear whether there is a substantial pool of patients who are contraindicated to both ranibizumab and aflibercept in clinical practice. The submission did not provide evidence to quantify the size of this population.

- Treatment failure with VEGF inhibitors (nominated comparator: placebo): It is unclear whether patients need to fail treatment with one or both of the VEGF inhibitors currently available. Available observational studies suggest the treatment effect may be smaller in patients with VEGF inhibitor resistant macular oedema than in the broader population recruited in the clinical trials. The ESC considered the submission had not provided unequivocal evidence that dexamethasone implant is an effective treatment for patients who have failed treatment with VEGF inhibitors. The ESC also noted that 2015 British Royal College of Ophthalmologists guidelines[1] (p.30) suggest "[i]f an anti-VEGF agent is stopped due to lack of efficacy, there is no randomised controlled trials that provide evidence that switching to another anti-VEGF agent may be effective. However, given our experience with switching anti-VEGF agents in neovascular age related macular degeneration, it may be worthwhile switching to another

[1] https://www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-RVO-Guidelines-July-2015.pdf

anti-VEGF agent." Thus, the ESC considered there is a limited clinical place for dexamethasone in this subgroup.

- Unsuitable for treatment with VEGF inhibitors (nominated comparators: VEGF inhibitors): This population is patients who want to avoid VEGF inhibitors due to the frequency of VEGF inhibitor injections (i.e. patient preference or logistical reasons). The ESC noted the clinical data indicates that dexamethasone implant is inferior to VEGF inhibitors in terms of efficacy and safety. Further, a significant proportion of patients in the dexamethasone treatment arms of these trials experienced a worsening of visual acuity over the treatment period, losing ≥15 letters best corrected visual acuity. The ESC considered that while treatment compliance with the VEGF inhibitors may have been an issue over the longer term treatment of DMO and thus justified the PBS listing of dexamethasone in this subgroup, this was less likely to be an issue for RVO for which macular oedema does not necessarily need prolonged treatment; thus there is no sound clinical reason for offering the alternative of dexamethasone (a less effective and more harmful therapy) in this subgroup.

2.5 The ESC noted the submission claimed that the PBS listing of dexamethasone implant for DMO was limited to patients with pseudophakic lenses due to better efficacy in this subgroup (the TGA indication is for the broader DMO population). In contrast, the submission noted no difference in efficacy between phakic and pseudophakic subgroups in retinal vein occlusion. Nevertheless, the ESC noted the risk: benefit profile of dexamethasone implant is better in pseudophakic than in phakic patients due to the increased risk of cataract formation in phakic eyes, which in turn can reduce visual acuity.

2.6 The TGA delegate's overview for dexamethasone implant for RVO (March 2017) noted that dexamethasone injection was associated with an increased risk of cataracts, which increased with dose and duration of treatment. It was also noted that the benefits of treatment were at the expense of an increased risk of cataracts and increased risk of raised intraocular pressure.

2.7 The most recent TGA AusPAR for dexamethasone (October 2016) noted that the best corrected visual acuity (BCVA) improvement in phakic eyes appears to be ill sustained due to the almost inevitable development of cataract. Optical coherence tomography (OCT) data appear similar in pseudophakic and phakic study eyes and BCVA improvement is restored following cataract surgery in phakic eyes. However, the data suggest that treatment of phakic eyes is largely ineffective, unless or until the patient has a lens replacement. Based on subgroup analyses of the two Phase III trials (in DMO), the Committee for Medicinal Products for Human Use (CHMP) considered that the benefit risk balance was favourable for the restricted patient population who were pseudophakic or insufficiently responsive or unsuitable for non-corticosteroid therapy. The ESC noted that 3-year trials exist for DMO, where an increase in cataract formation was noted from year 2-3 of treatment. The trials for

RVO were for six months, with a six month extension study.

2.8 Based on this increased risk, the ESC queried whether any PBS listing of dexamethasone implant in RVO should be consistent with that for DMO by excluding patients capable of developing cataracts, or whether there is sufficient reason to differentiate this risk between RVO and DMO, for example in relation to the expected duration therapy using dexamethasone implants.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 Dexamethasone implant was approved by the TGA on 16 June 2017 for macular oedema secondary to BRVO or CRVO.

Dexamethasone implant is also TGA registered for non-infectious uveitis affecting the posterior segment of the eye, and diabetic macular oedema.

4 Population and disease

4.1 Retinal vein occlusion is a common vascular disorder of the retina and one of the most common causes of vision loss worldwide. There are two major anatomic types of retinal vein occlusion: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). BRVO occurs when a vein in the distal retinal venous system is occluded, which leads to haemorrhage along the distribution of a small vessel of the retina. CRVO occurs due to a thrombus within the central retinal vein, leading to the involvement of the entire retina. Macular oedema is a frequent consequence of all forms of retinal vein occlusion and is the major cause of visual loss with this condition. The presentation is primarily unilateral.

4.2 The current first-line therapies for BRVO and CRVO are vascular endothelial growth factor (VEGF) inhibitors. Ranibizumab and aflibercept are currently PBS listed for macular oedema secondary to retinal vein occlusion. Treatment is episodic, performed until resolution of macular oedema is achieved.

4.3 The submission proposed that that there is a clinical need for dexamethasone implant in patients with macular oedema secondary to BRVO or CRVO for whom VEGF inhibitors are contraindicated, unsuitable, or the patient has failed prior treatment.

The dexamethasone implant enables the sustained release of dexamethasone, a potent corticosteroid that suppresses inflammation by inhibiting multiple inflammatory cytokines, over a number of weeks. This decreases fibrin deposition, capillary leakage, and migration of the inflammatory cells, which in turn reduces macular oedema.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated sham injection as a proxy for no active treatment as the main comparator when considering patients in whom VEGF inhibitors are contraindicated or have failed or are otherwise unsuitable. The ESC considered this to be an appropriate comparator for this population. Prior to the introduction of VEGF inhibitors, grid laser photocoagulation was the standard treatment for macular oedema associated with BRVO. Grid laser photocoagulation was considered as a comparator in the ranibizumab November 2013, March 2014, and July 2014 submissions for BRVO. The current place in therapy for grid laser photocoagulation remains in patients with BRVO who have failed treatment with a VEGF inhibitor, and thus may remain a secondary comparator for dexamethasone implant.

The submission nominated VEGF inhibitors as the main comparator when considering patients who could use a VEGF inhibitor, but in whom such treatment is not preferred or unsuitable (due to patient preference or logistical reasons relating to the frequency of VEGF inhibitor injections). The ESC considered this to be an appropriate comparator for this population. Other potential pharmacological therapies include triamcinolone acetonide, a pharmacological analogue of dexamethasone, and bevacizumab, another VEGF inhibitor. However the use of these agents for retinal vein occlusion is outside of their current approved indications.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The sponsor claimed the submission was made in response to requests from clinicians that dexamethasone implant be made available for RVO patients in Australia. The clinician at the hearing described the clinical need for dexamethasone implant in the context of VEGF inhibitors remaining the first-line treatment of choice. However, as these inhibitors represent a large treatment burden for some patients (up to approximately 25%) who require long-term therapy, dexamethasone implant would provide an option for less frequent treatments (e.g. every four months instead of potentially monthly) for these patients. If the treatment burden meant some patients were not adhering to the 4-weekly VEGF inhibitor treatment, the clinician claimed that it may be more beneficial to be treated less frequently with dexamethasone. The PBAC noted there was no clinical data to support this assertion and that the clinical data indicated that benefit with dexamethasone reduced after two months. The clinician further stated that the benefits of dexamethasone treatment outweighed the risk of cataract development in this patient group, given RVO patients do not often need repeated injections of dexamethasone and they are likely older patients who may have already had cataract surgery. The PBAC noted the pre-PBAC response (p2) further

supported the known risk: benefit profile for dexamethasone stating that, where a satisfactory level of resolution of RVO has not been achieved with VEGF inhibitors, clinicians would prefer to use dexamethasone implant, with its risk of cataract development (reversible by removal of the lens and replacement with an artificial lens), rather than permitting irreversible vision loss due to RVO. The PBAC considered that the information in the hearing was supported by the consumer comments, but did not substantively address how the choice to use dexamethasone in the proposed 'unsuitable' population would support best clinical practice, especially given the relatively short duration of treatment in RVO.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described treatment with dexamethasone implant as a desirable alternative for patients who respond poorly or are contraindicated to the current first line agents with the potential advantage of requiring less frequent injections, thus reducing treatment burden for patients and decreasing cost. The PBAC noted that further comments related to the less frequent injections being of benefit not just to the individual but also to the busy public hospital outpatient clinics. The PBAC was concerned that this signalled a potentially sub-optimal clinical decision being made should dexamethasone be prescribed for patients considered 'unsuitable' for VEGF inhibitors. Further clarity of what that criterion in the proposed PBS restriction means would be required.

Clinical trials

6.3 The submission was based on comparisons between dexamethasone implant and nominated comparators:

- Three head-to-head trials comparing dexamethasone implant to placebo (sham) in patients with CRVO or BRVO (GENEVA-008, GENEVA-009, Trial 020).
- Three head-to-head trials comparing dexamethasone implant to ranibizumab, a VEGF inhibitor, in patients with BRVO (COMO, COMRADE-B) or CRVO (COMRADE-C).

6.4 Details of the randomised trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Dexamethasone implant versus sham		
GENEVA 008	A Six-Month, Phase 3, Multicentre, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Study Number: 206207-008. 6-Month Report	November 2008

Trial ID	Protocol title/ Publication title	Publication citation
	A Six-Month, Phase 3, Multicentre, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Study Number: 206207-008. 12-Month Report	November 2009
GENEVA 009	A Six-Month, Phase 3, Multicentre, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion Study Number: 206207-009. 6-Month Report. A Six-Month, Phase 3, Multicentre, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion Study Number: 206207-009. 12-Month Report	November 2008 November 2009
GENEVA pooled results	Haller JA, Bandello F, Belfort Jr R, et al. Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion. Haller J, Bandello F, Belfort R, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Yeh W, Haller JA, Lanzetta P et al. Effect of the Duration of Macular Edema on Clinical Outcomes in Retinal Vein Occlusion Treated with Dexamethasone Intravitreal Implant. Kuppermann BD, Haller JA, Bandello F et al. Onset and Duration of Visual Acuity Improvement after Dexamethasone Intravitreal Implant in Eyes with Macular Edema Due to Retinal Vein Occlusion. Sadda S, Danis RP, Pappuru RR et al. Vascular changes in eyes treated with dexamethasone intravitreal implant for macular edema after retinal vein occlusion.	*Ophthalmology.* 2010; 117(6): 1134-1146 *Ophthalmology.* 2011; 118(12): 2453-2460 *Ophthalmology*. 2012; 119(6): 1190-1198 *Retina.* 2014;34(9): 1723-1749 *Ophthalmology.* 2013; 120(7): 1423-1431
Trial 020	A Six-Month, Phase 3, Multicentre, Masked, Randomized, Sham-Controlled Trial with a Two-Month Open-label Phase to Assess the Safety and Efficacy of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Li X, Wang N, Liang X, et al. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicentre study.	October 2014 *Graefe's Archive for Clinical and Experimental Ophthalmology.* 2018; 256:59-69
Dexamethasone implant versus ranibizumab		
COMO	A 12-Month, Multicentre, Randomised, Parallel Group Study to Compare the Efficacy and Safety of OZURDEX® Versus Lucentis® in Patients with Branch Retinal Vein Occlusion	September 2015
COMRADE-B	Hattenbach LO, Hoerauf H, Feltgen N, et al. Efficacy and Safety of 0.5 mg Ranibizumab Administered as Intravitreal Injections PRN Compared with Intravitreal Implant Containing 0.7 mg Dexamethasone in Patients with Branch Retinal Vein Occlusion Over 6 Months: The COMRADE-B Study.	*Ophthalmologica.* 2014; 232(Suppl.2): 90.

Trial ID	Protocol title/ Publication title	Publication citation
	Hattenbach LO, Feltgen N, Bertelmann T, et al. Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B).	*Acta Ophthalmologica* 2017; doi: 10.1111/aos.13381. [Epub ahead of print].
COMRADE-C	Hoerauf H, Feltgen N, Eter N, et al. Efficacy and Safety of 0.5 mg Ranibizumab Compared with Intravitreal Implant Containing 0.7 mg Dexamethasone in Patients with Central Retinal Vein Occlusion Over 6 Months: The COMRADE-C Study. Hoerauf H, Feltgen N, Weiss C, et al. Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE-C): a European Label Study.	*Ophthalmologica*. 2014; 232(Suppl.2):90. *American Journal of Ophthalmology.* 2016; 258-267.
COMRADE-Extension	Feltgen N, Bertelmann T. Safety and efficacy of ranibizumab 0.5 mg vs dexamethasone 0.7 mg intravitreal implant in patients with branch or central retinal vein occlusion: Long-term results of the COMRADE-Extension study.	*Association for Research in Vision and Ophthalmology (ARVO) 2016 Annual Meeting 2016.*

Source: Table 2.2.1, pp.25-27; Table 2.2.2, pp.27-28; Table 2.2.3, p.p.28-29 of the submission.
Note: Conference abstracts not included where full publications were available

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in economic evaluation
Dexamethasone implant versus placebo (sham)						
GENEVA-008	599	Multi-centre, randomised, blinded 6-month (plus 6-month open-label extension)	Low	Macular oedema secondary to retinal vein occlusion (BRVO/CRVO)	Time to achieve ≥15 letter improvement BCVA; Proportion of eyes with ≥15 letter improvement in BCVA at day 90	Not used
GENEVA-009	668	Multi-centre, randomised, blinded 6-month (plus 6-month open-label extension)	Low	Macular oedema secondary to retinal vein occlusion (BRVO/CRVO)	Proportion of eyes with ≥15 letter improvement in BCVA at day 180	Not used
Trial 020	262	Randomised, blinded 6-month (plus 2-month open-label extension)	Low	Macular oedema secondary to retinal vein occlusion (BRVO/CRVO)	Time to ≥15-letter improvement from baseline in BCVA	Not used
Dexamethasone implant versus ranibizumab						
COMO	307	Multi-centre, randomised, blinded 12-month	Unclear	Macular oedema secondary to BRVO	Mean change in BCVA at month 12 using ETDRS method	Average no. injections in year 1
COMRADE-B	244	Multi-centre, randomised, blinded 6-month	Unclear	Macular oedema secondary to BRVO	Mean average change in BCVA from baseline to month 1 through month 6	Not used
COMRADE-C	243	Multi-centre, randomised, blinded 6-month	Unclear	Macular oedema secondary to CRVO	Mean average change in BCVA from baseline to month 1 through month 6	Not used

Source: Table 2.3.1, pp.31-33; Table 2.3.2, pp.34-40 of the submission
Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; BCVA, best corrected visual acuity; DB, double blind; ETDRS, early treatment diabetic retinopathy study; MC, multi-centre; PC, placebo-controlled; R, randomised.

6.6 The submission acknowledged that the broader BRVO/CRVO populations included in the clinical trials may not be representative of the target PBS population who are

contraindicated to, unsuitable for, or who have failed VEGF inhibitors. Therefore, the submission also provided additional supportive observational data on the use of dexamethasone implant in the subgroup of patients who have previously failed VEGF therapy.

6.7 The majority of clinical trial evidence was based on a single implantation of the product (with the exception of the COMO trial which allowed 2-3 implants), which may not be sufficient to cover the duration of a macular oedema episode. Therefore the submission also provided additional supportive observational data of the efficacy and safety of multiple dexamethasone implantations.

6.8 The submission did not explicitly nominate a primary outcome. In the trials, treatment response was defined as 15 or more letters improvement from baseline best corrected visual acuity (BCVA). Visual acuity is commonly used as the primary outcome in trials and network meta-analyses of retinal vein occlusion, with a 15 or more letter change (equivalent to 3 lines or more on an ETDRS chart) generally considered clinically relevant. The PBAC has previously generally expressed a preference for changes of 10-15 letters in BCVA to be considered clinically important in retinal vein occlusion (e.g. ranibizumab PSD, March 2013; ranibizumab PSD, November 2013; aflibercept PSD, November 2014). However, the PBAC has also previously noted an increase of 5 letters or more might represent a clinically meaningful difference for some patients, but the clinical importance will also depend on the baseline visual acuity of each eye (ranibizumab PSD, March 2013).

6.9 The submission did not explicitly nominate a non-inferiority margin. The COMO trial comparing dexamethasone implant with ranibizumab used a 5-letter noninferiority margin. In the COMRADE trials, power calculations were performed based on a 6 letter difference. The PBAC has previously stated that 'a mean best corrected visual acuity change of -5 letters in the lower bound non-inferiority limit was probably reasonable' (paragraph 7.5, Dexamethasone implant PSD, March 2015).

Comparative effectiveness

6.10 Table 4 summarises the mean change in BCVA (number of letters gained) from baseline in the trials comparing dexamethasone implant with sham (GENEVA 008, GENEVA 009, and Trial 020).

Table 4: Change in best corrected visual acuity letters from baseline in GENEVA 008, GENEVA 009, and Trial 020: dexamethasone implant versus placebo (sham) in BRVO/CRVO

	GENEVA 008 (BRVO/CRVO)		GENEVA 009 (BRVO/CRVO)		Trial 020 (BRVO/CRVO)	
	DEX 700 (N=201)	Sham (N=202)	DEX 700 (N=226)	Sham (N=224)	DEX (N=129)	Sham (N=130)
Month 1						
Mean change from baseline to Month 1 (SD)	7.6 (9.3)	2.5 (9.4)	8.5 (9.8)	2.7 (8.4)	9.1 (8.5)	2.0 (9.3)
Mean difference in mean change from baseline to Month 1 (95% CI)	5.2 (3.4, 6.9)		5.8 (4.2, 7.4)		7.1 (4.9, 9.3)	
Month 2						
Mean change from baseline to Month 2 (SD)	9.5 (10.0)	3.1 (10.3)	10.1 (10.5)	3.2 (11.0)	10.6 (10.4)	1.7 (12.3)
Mean difference in mean change from baseline to Month 2 (95% CI)	6.4 (4.5, 8.4)		6.9 (5.0, 8.9)		8.9 (6.1, 11.6)	
Month 3						
Mean change from baseline to Month 3 (SD)	7.2 (10.8)	2.8 (10.8)	7.3 (12.0)	3.5 (11.9)	7.7 (12.7)	1.8 (13.0)
Mean difference in mean change from baseline to Month 3 (95% CI)	4.3 (2.2, 6.5)		3.9 (1.7, 6.0)		5.9 (2.8, 9.1)	
Month 6						
Mean change from baseline to Month 6 (SD)	4.6 (12.7)	2.7 (13.5)	5.5 (13.2)	2.5 (14.2)	3.2 (15.3)	4.0 (13.7)
Mean difference in mean change from baseline to Month 6 (95% CI)	1.9 (-0.7, 4.5)		3.0 (0.6, 5.4)		-0.7 (-4.1, 2.8)	

Source: Table 2.5.1, p.81 of the submission; clinical trial reports
Abbreviations: BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; DEX, dexamethasone implant; SD, standard deviation

6.11 The mean improvement in BCVA letters from baseline to month 1, 2, and 3 statistically significantly favoured dexamethasone implant over sham in all studies. The greatest change was measured at month 2, where the difference between treatment groups ranged from 6.4 to 8.9 letters. The clinical importance of this difference was unclear. The treatment efficacy of dexamethasone implant beyond three months is unclear given that the key clinical trials did not report results at Month 4 and Month 5 and the results at Month 6 were not consistent between trials. As a consequence, the appropriate implant frequency in clinical practice remains unclear.

6.12 The proportion of eyes gaining 15 or more letters in BCVA from baseline are summarised in Table 5.

Table 5: Proportion of eyes gaining ≥15 letters in best corrected visual acuity from baseline in GENEVA 008, GENEVA 009, and Trial 020: dexamethasone implant versus placebo (sham) in BRVO/CRVO

	GENEVA 008 (BRVO/CRVO)		GENEVA 009 (BRVO/CRVO)		Trial 020 (BRVO/CRVO)	
	DEX 700 (N=201)	Sham (N=202)	DEX 700 (N=226)	Sham (N=224)	DEX (N=129)	Sham (N=130)
Month 1						
Number (%) of patients with ≥15 letter gain in BCVA	40 (19.9)	15 (7.4)	51 (22.6)	17 (7.6)	37 (28.7)	7 (5.4)
Difference (95% CI)	12.5 (5.9, 19.1)		15.0 (8.5, 21.4)		23.3 (14.6, 32.0)	
Month 2						
Number (%) of patients with ≥15 letter gain in BCVA	58 (28.9)	21 (10.4)	67 (29.6)	27 (12.1)	45 (34.9)	15 (11.5)
Difference (95% CI)	18.5 (10.9, 26.0)		17.6 (10.3, 24.9)		23.3 (13.5, 33.2)	
Month 3						
Number (%) of patients with ≥15 letter gain in BCVA	45 (22.4)	25 (12.4)	48 (21.2)	31 (13.8)	43 (33.3)	17 (13.1)
Difference (95% CI)	10.0 (2.7, 17.3)		7.4 (0.4, 14.4)		20.3 (10.3, 30.2)	
Month 6						
Number (%) of patients with ≥15 letter gain in BCVA	39 (19.4)	37 (18.3)	53 (23.5)	38 (17.0)	30 (23.3)	27 (20.8)
Difference (95% CI)	1.1 (-6.6, 8.7)		6.5 (-0.9, 13.9)		2.5 (-7.6, 12.6)	

Source: Table 2.5.4, p.87 of the submission

Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; DEX, dexamethasone implant

6.13 The proportion of eyes which achieved a ≥15 letter change from baseline BCVA was greater in the dexamethasone implant group than in the sham group in each of the trials from month 1 to month 3. There was no statistically significant difference between groups at month 6. Overall, the proportion of eyes gaining ≥15 letters was low in both dexamethasone implant and sham treatment groups across trials.

6.14 In a pooled analysis of the GENEVA trials comparing dexamethasone implant with sham, treatment with dexamethasone implant was associated with a statistically significantly faster time to achieve an improvement of ≥15 letters BCVA from baseline (log-rank test p <0.001). At day 180, the cumulative response rate was 41% in the dexamethasone implant 700 µg group, and 23% in the sham group.

6.15 In Trial 020 comparing dexamethasone implant with sham, treatment with dexamethasone implant was associated with a statistically significantly faster time to achieve an improvement of ≥15 letters BCVA from baseline (log-rank test p <0.001). The estimated hazard ratio from a Cox regression model adjusted for baseline retinal vein occlusion diagnosis (BRVO or CRVO), age, and sex was 2.4 (95% CI: 1.6, 3.7).

6.16 There were no statistically significant improvements observed in the dexamethasone implant group compared with the sham group in the change from baseline to months 1, 2, 3 or 6 in the Visual Function Questionnaire-25 composite score in GENEVA-008 or GENEVA-009, or in the subscores reported in Trial 020.

6.17 Table 6 summarises the mean change in BCVA (number of letters gained) from baseline in the trials comparing dexamethasone implant with ranibizumab (COMO, COMRADE-B, and COMRADE-C).

Table 6: Change in best corrected visual acuity from baseline in COMO (BRVO), COMRADE-B (BRVO), and COMRADE-C (CRVO): dexamethasone implant versus ranibizumab

	COMO (BRVO)		COMRADE-B (BRVO)		COMRADE-C (CRVO)	
	DEX 700 (N=154)	RANI (N=153)	DEX (N=126)	RANI (N=118)	DEX (N=119)	RANI (N=124)
Baseline, mean (SD)	56.6 (10.9)	59.2 (10.9)	NR	NR	51.5 (15.6)	51.7 (16.5)
Month 3						
Mean change from baseline to Month 3 (SD)	10.0 (7.5)	12.8 (7.4)	9.3 (10.1)	16.2 (11.0)	7.0 (18.2)	16.0 (13.4)
Mean difference in mean change from baseline to Month 3 (95% CI)	-2.8 (-4.5, -1.1)		-6.9 (-4.2, -9.6)		-9.0 (-5.0, -13.0)	
Month 6						
Mean change from baseline to Month 6 (SD)	9.0 (8.7)	14.8 (8.7)	9.2 (12.5)	17.3 (11.8)	-3.2 (NR)	14.8 (NR)
Mean difference in mean change from baseline to Month 6 (95% CI)	-5.8 (-7.6, -3.9)		-8.1 (-11.0, -5.2)		-17.96 (-22.5, -13.4)	
Month 9						
Mean change from baseline to Month 9 (SD)	9.6 (9.9)	15.3 (8.7)	N/A	N/A	N/A	N/A
Mean difference in mean change from baseline to Month 9 (95% CI)	-5.7 (-7.8, -3.7)		N/A		N/A	
Month 12						
Mean change from baseline to Month 12 (SD)	9.3 (8.7)	15.5 (8.7)	N/A	N/A	N/A	N/A
Mean difference in mean change from baseline to Month 12 (95% CI)	-6.3 (-8.3, -4.2)		N/A		N/A	

Source: Table 2.5.7, pp.92-93 of the submission; COMO clinical trial report; Hattenbach et al. (2017); Hoerauf et al. (2016).
Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX, dexamethasone implant; RANI, ranibizumab; SD, standard deviation; CI, confidence interval; NR, not reported; N/A, not assessed
Note: standard deviations were calculated for the COMO trial during the evaluation.

6.18 Overall ranibizumab achieved statistically significantly greater increases in BCVA letters gained than dexamethasone implant at all time points.

6.19 In the COMO trial, dexamethasone implant was inferior to ranibizumab using a lower bound noninferiority margin of -5 letters at months 6, 9 and 12.

6.20 The COMO and COMRADE-B trials were both conducted in patients with BRVO, and COMO allowed eligible patients to receive a repeat dexamethasone implant at 5 months. The treatment effect of dexamethasone implant and ranibizumab at 6 months in these trials was similar.

6.21 In the COMRADE-B and COMRADE-C trials, the between-group differences favoured ranibizumab. At month 3, improvement in mean BCVA was statistically significantly higher with ranibizumab compared to dexamethasone intravitreal implant. This difference between the treatment groups further increased until month 6. Dexamethasone implant did not appear to be as effective in CRVO, with patients in

this treatment arm losing visual acuity on average by month 6 in the COMRADE-C trial. The ESC considered that this was consistent with the waning of clinical response with dexamethasone implant beginning at approximately 8-12 weeks.

6.22 The proportion of eyes gaining ≥10 or ≥15 letters in BCVA from baseline are summarised in Table 7.

Table 7: Proportion of eyes gaining ≥10 or ≥15 letters in best corrected visual acuity from baseline in COMO (BRVO), COMRADE-B (BRVO), and COMRADE-C (CRVO): dexamethasone implant versus ranibizumab

	COMO (BRVO)		COMRADE-B (BRVO)		COMRADE-C (CRVO)	
	DEX 700 (N=154)	RANI (N=153)	DEX (N=126)	RANI (N=118)	DEX (N=119)	RANI (N=124)
Month 6						
Number (%) of patients with ≥15 letter gain in BCVA	NR	NR	47 (37.3)	72 (61.1)	22 (18.5)	73 (58.9)
Difference %, p-value	NR		-23.8, p=0.0002		-40.4, p<0.001	
Number (%) of patients with ≥10 letter gain in BCVA	NR	NR	67 (53.4)	91 (77.0)	38 (31.9)	89 (71.8)
Difference %, p-value	NR		-23.6, p<0.0001		-39.9, p<0.0001	
Month 12						
Number (%) of patients with ≥15 letter gain in BCVA	52 (33.8)	91 (59.5)	N/A	N/A	N/A	N/A
Difference, % (p-value)	-25.7, p<0.0001		N/A		N/A	
Odds ratio (95% CI)	0.3 (0.18, 0.48)		N/A		N/A	
Number (%) of patients with ≥10 letter gain in BCVA	79 (51.3)	112 (73.2)	N/A	N/A	N/A	N/A
Difference, % (p-value)	-21.9, p<0.0001		N/A		N/A	
Odds ratio (95% CI)	0.3 (0.20, 0.55)		N/A		N/A	

Source: Table 2.5.8, p.95 of the submission; Table 14.2.3.1, COMO clinical trial report
Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX, dexamethasone; RANI, ranibizumab; NR, not reported; N/A, not assessed

6.23 Results of the COMO, COMRADE-B, and COMRADE-C studies show that ranibizumab results in higher proportions of patients with clinically important visual acuity gains. These were statistically significantly higher than those achieved with dexamethasone intravitreal implant at all time points assessed in the trials.

6.24 Change in Visual Function Questionnaire composite (or subscores where composite was not reported) from baseline to month 6 were reported for the dexamethasone versus ranibizumab treatment arms in COMO and COMRADE-C. Treatment with ranibizumab was associated with statistically significantly larger improvements in quality of life compared to dexamethasone implant in the COMO trial. Similar results were also reported in the COMRADE-C trial. No quality-of-life data were presented for the COMRADE-B trial.

6.25 Results from the COMO trial, open label extension studies of the GENEVA and COMRADE trials, and nonrandomised studies, which allowed reimplantation of dexamethasone, suggest a similar magnitude of response in terms of visual acuity

after the second implant compared to the initial implant. This did not address the key issue of how many additional implants might be needed for a course of therapy.

6.26 The submission presented the results of nine nonrandomised studies which examined the effectiveness of dexamethasone implant in patients who had previously failed treatment with VEGF inhibitors. The results indicated that some patients who have previously failed VEGF inhibitor therapy may experience some improvement in BCVA whilst receiving dexamethasone implant. However, due to the observational study design it is unclear whether this was due to the treatment effect of dexamethasone implant. Overall the treatment effect across studies was highly variable. Reported BCVA changes in the failed population appeared to be generally smaller than those reported in the broader retinal vein occlusion population. Overall, it remains unclear whether dexamethasone implant is superior to no therapy in patients who have failed treatment with a VEGF inhibitor.

6.27 The submission claimed that no studies could be located investigating the use of VEGF inhibitors in patients who were contraindicated, unsuitable or had failed prior treatment with VEGF inhibitors. This claim was not reasonable given that there are a number of published studies available reporting the effectiveness of switching VEGF inhibitors (e.g. from ranibizumab to aflibercept, which each inhibit VEGF via differing mechanisms).

Comparative harms

6.28 Overall, the incidence of adverse events reported in the randomised trials was consistent with the known safety profile of dexamethasone implant.

6.29 Ocular adverse events (including increases in intraocular pressure, ocular hypertension, and cataract) were reported in a higher proportion of patients in the dexamethasone treatment arm compared to the sham arm in each of the trials comparing dexamethasone implant with placebo. There was no difference in the proportion of patients discontinuing due to adverse events between treatment arms in these trials.

6.30 The incidence of ocular adverse events (including increases in intraocular pressure and ocular hypertension) was higher in the dexamethasone implant treatment arms than the ranibizumab treatment arms across all trials comparing dexamethasone implant with ranibizumab. A higher incidence of cataract was observed in the COMO trial, which had a longer duration (12 months) and allowed repeat administrations of dexamethasone implant compared with the COMRADE trials, which were each conducted over 6 months and evaluated a single dexamethasone implant.

6.31 There were higher incidences of adverse events overall in the COMRADE-C trial than the COMRADE-B trial, reflecting differences associated with BRVO and CRVO. CRVO is typically more severe and is less likely to resolve spontaneously. The incidence of discontinuation due to adverse events was greater in the dexamethasone implant treatment arms than the ranibizumab treatment arms across all trials.

6.32 Safety results from studies which allowed reimplantation with dexamethasone, were consistent with the randomised trials and the known safety profile of dexamethasone implant. Adverse events included increases in intraocular pressure and ocular hypertension, glaucoma, and cataracts.

6.33 Based on an expanded assessment of harms, important identified risks associated with dexamethasone implant include glaucoma, ocular hypertension, increased intraocular pressure, cataract formation, vitreous haemorrhage/ detachment, device dislocation and implant misplacement.

Benefits/harms

6.34 A summary of the comparative benefits and harms for dexamethasone implant versus placebo (sham) is presented in Table 8.

Table 8: Summary of comparative benefits and harms for dexamethasone implant versus placebo (sham) in BRVO/CRVO

Benefits				
Trial	**Event**	**Dexamethasone**	**Placebo (sham)**	**Mean difference (95% CI)**
GENEVA 008	Mean number of letters of BVCA gained from baseline to Month 3	7.2	2.8	4.3 (2.2, 6.5)
GENEVA 009		7.3	3.5	3.9 (1.7, 6.0)
Trial 020		7.7	1.8	5.9 (2.8, 9.1)
GENEVA 008	Mean number of letters of BVCA gained from baseline to Month 6	4.6	2.7	1.9 (-0.7, 4.5)
GENEVA 009		5.5	2.5	3.0 (0.6, 5.4)
Trial 020		3.2	4.0	-0.7 (-4.1, 2.8)
GENEVA 008	Patients who achieved a ≥15 letter BCVA improvement at Month 3, n/N (%)	45/201 (22.4)	25/202 (12.4)	10.0% (2.7, 17.3)
GENEVA 009		48/226 (21.2)	31/224 (13.8)	7.4% (0.4, 14.4)
Trial 020		43/129 (33.3)	17/130 (13.1)	20.3% (10.3, 30.2)
GENEVA 008	Patients who achieved a ≥15 letter BCVA improvement at Month 6, n/N (%)	39/201 (19.4)	37/202 (18.3)	1.1% (-6.6, 8.7)
GENEVA 009		53/226 (23.5)	38/224 (17.0)	6.5% (-0.9, 13.9)
Trial 020		30/129 (23.3)	27/130 (20.8)	2.5% (-7.6, 12.6)

Harms			
Trial	**Event**	**Dexamethasone**	**Placebo (sham)**
GENEVA 008	Intraocular pressure increased, n/N (%)	46/196 (23.5)	6/202 (3.0)
GENEVA 009		60/225 (26.7)	5/221 (2.3)
Trial 020		38/129 (29.5)	4/130 (3.1)
GENEVA 008	Conjunctival haemorrhage, n/N (%)	39/196 (19.9)	26/202 (12.9)
GENEVA 009		46/225 (20.4)	37/221 (16.7)
Trial 020		24/129 (18.6)	5/130 (3.8)
GENEVA 008	Cataract, n/N (%)	4/196 (2.0)	2/202 (1.0)
GENEVA 009		11/225 (4.9)	5/221 (2.3)
Trial 020		NR	NR
GENEVA 008	Ocular hypertension, n/N (%)	7/196 (3.6)	2/202 (1.0)
GENEVA 009		10/225 (4.4)	2/221 (0.9)
Trial 020		4/129 (3.1)	0/130 (0.0)

Source: Table 2.5.1, p.81 of the submission; Table 2.5.4, p.87 of the submission; Table 2.6.4, pp.112-113; Table 2.6.5, p.113-114; Table 2.6.6, p.114 of the submission; associated clinical trial reports

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; NR, not reported

Note: GENEVA 008 trial, GENEVA 009 trial and Trial 020 were conducted in mixed patient populations with central or branch retinal vein occlusion.

6.35 Across all trials, treatment response was considered to be an improvement of 15 or more letters from baseline in the study eye.

6.36 On the basis of the direct evidence presented in the submission:

- Patients treated with a single dexamethasone implant would have a greater improvement in visual acuity compared with no treatment at 3 months, with the average patient gaining an additional 4 to 6 letters, and at 6 months, an additional 0 to 3 letters.
- For every 100 patients treated with a single dexamethasone implant compared with no treatment there would be approximately 7 to 20 additional patients who achieve an improvement of 15 letters or more on a standard eye chart at 3 months and no difference at 6 months.
- For every 100 patients treated with a single dexamethasone implant compared to no treatment, there would be over a period of 6 months:
    - Approximately 21 to 26 additional patients with increased intraocular pressure;
    - Approximately 4 to 15 additional patients with conjunctival haemorrhage;
    - Approximately 1 to 3 additional patients with cataract;
    - Approximately 3 to 4 additional patients with ocular hypertension.

6.37 A summary of the comparative benefits and harms for dexamethasone implant versus ranibizumab intravitreal injection is presented in Table 9.

Table 9: Summary of comparative benefits and harms for dexamethasone versus ranibizumab in COMO (BRVO), COMRADE-B (BRVO), and COMRADE-C (CRVO)

Benefits				
Trial	**Event**	**Dexamethasone**	**Ranibizumab**	**Mean difference (95% CI)**
COMO	Mean number of letters of BVCA gained from baseline to Month 3	10.0	12.8	-2.8 (-4.5, -1.1)
COMRADE-B		9.3	16.2	-6.9 (-4.2, -9.6)
COMRADE-C		7.0	16.0	-9.0 (-5.0, -13.0)
COMO	Mean number of letters of BVCA gained from baseline to Month 6	9.0	14.8	-5.8 (-7.6, -3.9)
COMRADE-B		9.2	17.3	-8.1 (-11.0, -5.2)
COMRADE-C		-3.2	14.8	-18.0 (-22.5, -13.4)
COMO	Patients who achieved a ≥15 letter BCVA improvement at Month 6, n/N (%)	NR	NR	NR
COMRADE-B		47/126 (37.3)	72/118 (61.1)	-23.8%, p=0.0002
COMRADE-C		22/119 (18.5)	73/124 (58.9)	-40.4%, p<0.001
COMO	Patients who achieved a ≥15 letter BCVA improvement at Month 12, n/N (%)	52/154 (33.8)	91/153 (59.5)	-25.7%, p<0.0001
COMRADE-B		N/A	N/A	N/A
COMRADE-C		N/A	N/A	N/A
COMO	Patients who lost ≥15 letters of BCVA at Month 6, n/N (%)	NR	NR	NR
COMRADE-B		(5.1)	(0)	5.1%
COMRADE-C		31/119 (26.1)	1/124 (0.8)	25.3%, p<0.0001
COMO	Patients who lost ≥15 letters of BCVA at Month 12, n/N (%)	14/154 (9.1)	1/153 (0.7)	8.4%, p=0.0008
COMRADE-B		N/A	N/A	N/A
COMRADE-C		N/A	N/A	N/A

Harms			
Trial	**Event**	**Dexamethasone**	**Ranibizumab**
COMO	Intraocular pressure increased, n/N (%)	50/153 (32.7)	16/150 (10.7)
COMRADE-B		17/118 (14.4)	2/126 (1.6)
COMRADE-C		38/119 (31.9)	7/124 (5.6)
COMO	Conjunctival haemorrhage, n/N (%)	28/153 (18.3)	17/150 (11.3)
COMRADE-B		1/118 (0.8)	1/126 (0.8)
COMRADE-C		13/119 (10.9)	16/124 (12.9)
COMO	Cataract, n/N (%)	13/153 (8.5)	2/150 (1.3)
COMRADE-B		1/118 (0.8)	1/126 (0.8)
COMRADE-C		NR	NR
COMO	Ocular hypertension, n/N (%)	9/153 (5.9)	1/150 (0.7)
COMRADE-B		NR	NR
COMRADE-C		6/119 (5.0)	0/124 (0.0)

Source: Table 2.5.7, pp.92-93 of the submission; COMO clinical trial report; Hattenbach et al. (2017); Hoerauf et al. (2016); Table 2.5.8, p.95 of the submission; Table 14.2.3.1, COMO clinical trial report; Supplemental figure 2, Hattenbach et al. (2017); Supplemental figure 2, Hoerauf et al. (2016); Table 2.6.4, pp.112-113; Table 2.6.5, p.113-114; Table 2.6.6, p.114 of the submission
Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; NR, not reported; N/A, not assessed

6.38 Based on the direct evidence presented in the submission for the COMO trial (assessing multiple dexamethasone injections in BRVO):

- Patients treated with an average 2.5 dexamethasone implants over 12 months would have a smaller improvement in visual acuity compared with patients treated with an average 8.1 injections of ranibizumab, with the average patient having 2.8 fewer letters at 3 months and 6.0 fewer letters at 6 months.
- For every 100 patients treated with dexamethasone implant compared with ranibizumab over 12 months:

  - There would be approximately 26 fewer patients who achieve an improvement of 15 letters or more on a standard eye chart;
  - There would be approximately 8 additional patients who lose 15 letters or more on a standard eye chart.
- For every 100 patients treated with dexamethasone implant compared to ranibizumab, there would be over a period of 12 months:
  - Approximately 22 additional patients with increased intraocular pressure;
  - Approximately 7 additional patients with conjunctival haemorrhage;
  - Approximately 7 additional patients with cataract;
  - Approximately 5 additional patients with ocular hypertension.

6.39 Based on the direct evidence presented in the submission for the COMRADE-B trial (assessing single dexamethasone injection in BRVO patients):

- Patients treated with a single dexamethasone implant would have a smaller improvement in visual acuity compared with patients treated with monthly administrations of ranibizumab, with the average patient having 6.9 letters less at 3 months and 8.1 letters less at 6 months.
- For every 100 patients treated with dexamethasone implant compared with ranibizumab over 6 months:
  - There would be approximately 24 fewer patients who achieve an improvement of 15 letters or more on a standard eye chart;
  - There would be approximately 5 additional patients who lose 15 letters or more on a standard eye chart.
- For every 100 patients treated with dexamethasone implant compared to ranibizumab, there would be over a period of 6 months:
  - Approximately 13 additional patients with increased intraocular pressure;
  - No observable difference for conjunctival haemorrhage;
  - No observable difference for cataract;

6.40 Based on the direct evidence presented in the submission for the COMRADE-C trial (assessing single dexamethasone injection in CRVO patients):

- Patients treated with a single dexamethasone implant would have a smaller improvement in visual acuity compared with patients treated with monthly administrations of ranibizumab, with the average patient having 9.0 fewer letters at 3 months and 18.0 fewer letters at 6 months.
- For every 100 patients treated with dexamethasone implant compared with ranibizumab over 6 months:
  - There would be approximately 40 fewer patients who achieve an improvement of 15 letters or more on a standard eye chart;

  - There would be approximately 25 additional patients who lose 15 letters or more on a standard eye chart.
- For every 100 patients treated with dexamethasone implant compared to ranibizumab, there would be over a period of 6 months:
  - Approximately 26 additional patients with increased intraocular pressure;
  - Approximately 2 fewer patients with conjunctival haemorrhage;
  - Approximately 5 additional patients with ocular hypertension.

Clinical claim

6.41 The submission described dexamethasone implant as superior in terms of effectiveness compared with placebo (sham), and inferior in terms of safety. The ESC considered that these claims were reasonable, although the benefits were modest and the duration of therapy needed to be considered. Dexamethasone implant was superior in terms of efficacy to placebo at 2 and 3 months after administration, but not at 6 months. The PBAC agreed with the ESC advice.

6.42 The submission described dexamethasone implant as inferior in terms of effectiveness compared with ranibizumab, and inferior in terms of safety. The ESC considered that these claims were reasonable. The PBAC agreed with the ESC advice.

6.43 The ESC considered that the use of dexamethasone implant as an alternative to VEGF inhibitors was not adequately justified and should be considered in the context of the potential risks associated with dexamethasone implant, including the requirement of monitoring for and management of elevated intraocular pressure, and the inferior treatment effect in terms of visual acuity compared with VEGF inhibitors. The PBAC agreed with the ESC advice.

Economic analysis

6.44 Based on the pragmatic approach adopted by the PBAC for the dexamethasone DMO submission, the submission requested that PBAC consider whether the lower cost of dexamethasone versus comparators represents a sufficient discount to account for the worse efficacy and safety of dexamethasone implants compared to VEGF inhibitors in RVO patients. As stated above, the ESC did not consider that the residual unmet clinical need in RVO was analogous with that in DMO, based on the likely differences in frequency of administrations and duration of therapy, and therefore considered that this previous pragmatic approach did not necessarily apply for RVO.

6.45 The submission only presented a limited economic analysis for dexamethasone compared with VEGF inhibitors, relevant for the population who could use a VEGF inhibitor, but for whom such treatment is not preferred or unsuitable. No economic analysis was presented for the comparison of dexamethasone implant versus no active treatment in patients in whom VEGF inhibitors are contraindicated or have failed or are otherwise unsuitable. The cost effectiveness of dexamethasone

compared to no active treatment in RVO is unknown. The ESC noted the PSCR (p3) argued that the vision gain with dexamethasone in patients with RVO is similar to that in patients with DMO and pseudophakia, and therefore the cost-effectiveness will be no worse in RVO than in DMO. The ESC considered that this did not account for the differences in frequency of administrations and duration of therapy across DMO and RVO, and that the cost-effectiveness of dexamethasone compared to no active treatment in RVO remained unknown.

6.46 The submission presented a simple per patient cost analysis comparing dexamethasone implant with ranibizumab as a proxy for VEGF inhibitors over 3, 6, 12, and 36 months. The analysis did not link the reduced costs of using dexamethasone implant to a reduced set of clinical outcomes versus ranibizumab (i.e. cost savings per unit of benefit foregone). Thus the cost effectiveness of dexamethasone implant compared with VEGF inhibitors in RVO is unknown.

6.47 The submission justified this approach by stating that it aligned with the approach used for DMO (dexamethasone implant PSD, March 2016).

6.48 The effective price of ranibizumab was unknown to the sponsor, and was therefore estimated for the purposes of the cost analysis.

6.49 The cost analysis included costs associated with the monitoring and treatment of increased intraocular pressure associated with drug treatment. These costs were small and did not have a large impact on the cost analysis. It is unclear how regularly monitoring for increases in intraocular pressure would occur in practice. These may have been underestimated in the submission (1 visit in the first 6 months, 2.5 visits in the first 12 months, and 6.5 total visits over 3 years). The increasing proportion of patients likely to experience increases in intraocular pressure with subsequent dexamethasone implants, noted in the GENEVA-extension study, was not taken into account. Other adverse events known to be associated with dexamethasone implant, particularly over increasing periods of time such as glaucoma and cataract, were not considered in the cost analysis.

6.50 The submission claimed that injection frequencies at 3 and 6 months were based on the COMRADE and COMO trials. The 3 month estimates were consistent with product information documents for initial dosing, but were insufficient to adequately capture more flexible dosing intervals for retreatments. However, 6 month injection frequencies do not appear to be consistent with either COMO (1.9 dexamethasone injections to 5.9 ranibizumab injections) or COMRADE trials (1:4.7 in COMRADE B; 1:4.5 in COMRADE C).

6.51 At 12 months, the estimates were based on the COMO trial comparing dexamethasone implant and ranibizumab; and injection frequencies over 3 years were based on estimates previously accepted by PBAC for dexamethasone and ranibizumab in diabetic macular oedema.

6.52 The proposed substitution rates were highly uncertain due to a number of issues:

- In the COMRADE trials, patients received a single dexamethasone injection over the six month time period, whereas ranibizumab dosing was consistent with clinical practice.
- The retreatment time period in the COMO trial for dexamethasone implant was fixed (first retreatment for eligible patients was at 5 months, and a second retreatment at 10-11 months). This may not reflect retreatment rates in clinical practice given that the treatment effect of dexamethasone implant begins to wane from 8-12 weeks based on evidence from the clinical trials presented in the submission. Retreatment may thus occur more frequently than estimated using the COMO trial.
- The COMO trial used to estimate frequency of administrations was conducted only in patients with BRVO, which is known to have a higher likelihood of spontaneous resolution over the first three months and less severe visual acuity decrements compared to CRVO and thus may not be generalisable to the entire RVO population.
- The injection frequencies for dexamethasone implant and VEGF inhibitors previously accepted by PBAC for DMO may not be applicable to macular oedema due to RVO.
- Injection frequencies for ranibizumab, the comparator in the clinical trials, were assumed to be equivalent to rates for all VEGF inhibitors, which is consistent with previous therapeutic relativities considered by the PBAC for VEGF inhibitors (paragraph 6.27, dexamethasone March 2016 PSD; aflibercept March 2014 PSD) but is inconsistent with dosing frequencies stated in product information documents.

6.53 The PBAC previously considered that the approach taken in estimating the "equi-effective" frequency of administrations of dexamethasone implants compared with VEGF inhibitor injections in a given time period was unreliable due to problems with the sample size, exchangeability and applicability of the data sources (dexamethasone PSD, March 2016).

6.54 The results of the per patient cost analysis are summarised in Table 10.

Table 10: Summary of the results of the per patient cost analysis of dexamethasone implant versus VEGF inhibitors at 3, 6, 12, and 36 months

	Dexamethasone implant	VEGF inhibitor injection	Difference (dexamethasone implant vs VEGF inhibitor)
Effective DPMQ per administration	$[redacted]	$[redacted]	
Drug costs over 3 months			
Average number of administrations over 3 months	[redacted]	[redacted]	[redacted]
Total drug costs per patient over 3 months	$[redacted]	$[redacted]	-$[redacted]
Total costs for monitoring and managing adverse events over 3 months	$[redacted]	$[redacted]	$[redacted]
Total costs over 3 months excluding MBS administration costs:	$[redacted]	$[redacted]	-$[redacted]
Drug costs over 6 months			
Average number of administrations over 6 months	[redacted]	[redacted]	[redacted]
Total drug costs per patient over 6 months	$[redacted]	$[redacted]	-$[redacted]
Total costs for monitoring and managing adverse events over 6 months	$[redacted]	$0.00	$[redacted]
Total costs over 6 months excluding MBS administration costs:	$[redacted]	$[redacted]	-$[redacted]
Drug costs over 12 months			
Average number of administrations over 12 months	[redacted]	[redacted]	[redacted]
Total drug costs per patient over 12 months	$[redacted]	$[redacted]	-$[redacted]
Total costs for monitoring and managing adverse events over 12 months	$[redacted]	$0.00	$[redacted]
Total costs over 12 months excluding MBS administration costs:	$[redacted]	$[redacted]	-$[redacted]
Drug costs over 3 years			
Average number of administrations over 3 years	[redacted]	[redacted]	[redacted]
Total drug costs per patient over 3 years	$[redacted]	$[redacted]	-$[redacted]
Total costs for monitoring and managing adverse events over 3 years	$[redacted]	$0.00	$[redacted]
Total costs over 36 months (3 years) excluding MBS administration costs:	$[redacted]	$[redacted]	-$[redacted]

Source: Table 3.4.1, p.140; Table 3.5.1, p.141; Table 3.6.1, p.142; Table 3.7.1, p.143 of the submission; 'Economic and financial analyses- dexamethasone implant RVO March 2018.xls'

6.55 The cost analysis was presented with and without MBS costs for administration (intravitreal injection procedure and specialist attendance). Previously the PBAC determined that not including MBS costs in the calculation of the price was reasonable as a pragmatic approach in DMO (paragraph 6.34, Dexamethasone PSD, March 2016).

6.56 Overall, whilst the cost analyses presented in the submission suggested that dexamethasone implant would be cost saving compared to VEGF inhibitors over 3, 6, 12, and 36 months, these estimates were subject to significant uncertainty, particularly around frequency of administrations and adverse event costs.

6.57 These estimates failed to take into account the cost-effectiveness of dexamethasone implant in terms of clinical outcomes. The efficacy of dexamethasone implant lies somewhere between that of sham and that of ranibizumab. Without an economic analysis that values the clinical outcomes presented in the submission (e.g. cost per patient achieving a clinically important improvement in BCVA or deriving a cost per QALY), it is unclear whether dexamethasone implant is of acceptable cost-effectiveness compared with VEGF inhibitors.

6.58 The submission did not present any sensitivity analyses, however there are a number of sources of uncertainty which need to be considered when interpreting the results of the cost-analysis, and which may have a large impact on the results. Of particular concern are the relative injection frequencies for dexamethasone implant and VEGF inhibitors which will be affected by the treatment effect duration and intervals of repeat treatment of dexamethasone implant in clinical practice.

For more detail on PBAC's view, see section 7 PBAC outcome.

Drug cost/patient/year

6.59 The submission's estimated annual drug cost for dexamethasone implant was $[redacted], based on 2.5 implants per year at a proposed effective price of $[redacted]. The number of implants was based on the mean number of implants used in the 12-month COMO trial comparing dexamethasone implant and ranibizumab. This may not reflect rates of use of dexamethasone implant in practice given the fixed retreatment periods in the trial.

6.60 The submission's estimated annual drug cost for ranibizumab was $[redacted], based on 8.1 injections per year at an assumed effective price of $[redacted]. The number of injections was based on the mean number of injections used in the 12-month COMO trial comparing dexamethasone implant and ranibizumab. This may not reflect the long-term injection frequency of ranibizumab which switches from monthly dosing to as-needed dosing after 6 months of therapy.

Estimated PBS usage & financial implications

6.61 This submission was considered by DUSC. The submission used a market share approach to estimate the utilisation and financial implications associated with PBS listing of dexamethasone implant for the treatment of macular oedema secondary to BRVO or CRVO in patients who are contraindicated, unsuitable or have failed prior treatment with VEGF inhibitors.

6.62 The approach assumed that the total RVO market is captured by script utilisation for VEGF inhibitors, not accounting for market growth due to dexamethasone use in patients who cannot use VEGF inhibitors for any reason (i.e. the target population). The evaluation considered that it was unclear whether the substantial cost offsets associated with the substitution of VEGF inhibitors will be realised in practice given the target population of patients with RVO for whom a VEGF inhibitor is unsuitable

or those failing VEGF inhibitor. Such patients are unlikely to generate any cost offsets from reduced use of VEGF inhibitors.

Table 11: Estimated utilisation and cost to the PBS in the first six years of listing

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated dexamethasone utilisation and costs						
Market size (scripts for RVO)[a]						
Uptake rate	%	%	%	%	%	%
Total scripts						
PBS/RPBS cost (list DPMQ $1,354.79 per implant)	$	$	$	$	$	$
Patient copayment ($18.95)	-$	-$	-$	-$	-$	-$
Estimated rebate (%)[b]	-$	-$	-$	-$	-$	-$
PBS/RPBS cost after rebate	$	$	$	$	$	$
Additional cost of anti-glaucoma medications[c]	$	$	$	$	$	$
Estimated VEGF inhibitor utilisation and costs substituted by dexamethasone						
Total scripts (scripts per dexamethasone script)						
VEGF substitution cost offset (list DPMQ $)	$	$	$	$	$	$
Patient copayment ($18.95)	-$	-$	-$	-$	-$	-$
Estimated rebate (%)[d]	-$	-$	-$	-$	-$	-$
VEGF substitution cost offset after rebate	$	$	$	$	$	$
Net PBS/RPBS cost	**-$**	**-$**	**-$**	**-$**	**-$**	**-$**
Dexamethasone administration costs (1 intravitreal injection plus 1 consultation, $)	$	$	$	$	$	$
Dexamethasone additional monitoring costs (3 visits per implant, $)	$	$	$	$	$	$
VEGF cost offset (2.31 intravitreal injections and consultations, $ per substituted VEGF script)[e]	-$	-$	-$	-$	-$	-$
Total cost to government	**-$**	**-$**	**-$**	**-$**	**-$**	**-$**

Source: pp158-165 and 'Economic and financial analyses – dexamethasone implant RVO March 2018' Excel workbook of the submission
Abbreviations: IOP, intraocular pressure; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor inhibitor
a Based on 10% Medicare Sample analysis of ranibizumab and aflibercept scripts for branch and central retinal vein occlusion
b Rebate estimated as $ - $18.95 (average patient co-payment for ranibizumab and afilbercept for diabetic macular oedema) * % rebate on government expenditure
c Calculated based on 22.6% of dexamethasone scripts, 6 scripts per dexamethasone scripts and weighted DPMQ $ less $18.95 copayment
d Assumed to be the same for ranibizumab and aflibercept in the submission
e The MBS cost offsets associated with VEGF inhibitors were incorrectly estimated using the 100% schedule fee which was inconsistent with 85% rebate amount used to estimate MBS costs for dexamethasone

The redacted table shows that at year 6, the estimated number of scripts is 10,000 – 50,000 and the net saving to the PBS would be less than $10 million per year.

6.63 The proposed listing of dexamethasone implant on the PBS/RPBS for macular oedema secondary to branch or central retinal vein occlusion was estimated to result in cost savings of up to less than $10 million in the sixth year of listing ($10 - $20 million based on published prices). The estimated cumulative cost savings to the PBS/RPBS over six years was $10 - $20 million ($60 - $100 million based on published prices).

6.64 The proposed listing was associated with additional costs to non-PBS government expenditure due to adverse events (glaucoma, medication costs only) and additional monitoring costs. The proposed listing was also associated with cost savings due to a reduction in administration costs associated with substitution of VEGF inhibitors. The estimated cumulative cost savings to government was $30 - $60 million over six years ($60 - $100 million based on published prices).

6.65 The DUSC considered the submission's use of a market share approach, assuming that the use of dexamethasone as a second line treatment will substitute for existing listings of VEGF inhibitors, is inappropriate. As the introduction of dexamethasone will not reduce the use of first line therapy with VEGF inhibitors, its listing is likely to result in a net cost to government and not cost savings as estimated by the sponsor.

Quality use of medicines

6.66 DUSC commented that if the drug is marketed as an alternative for VEGF inhibitors in non-compliant patients for whom less frequent treatments may be beneficial, many of these patients will then need to be treated for intraocular pressure (IOP). DUSC considered it is a QUM issue for non-compliant patients to require additional therapy for adverse events.

Financial management – risk sharing arrangements

6.67 The PBAC noted the pre-PBAC response offered to address the potential financial issues by entering a risk share arrangement [redacted]

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC outcome

7.1 The PBAC recommended extending the listing of dexamethasone intravitreal injection 700 micrograms as an Authority required benefit for patients with CRVO or BRVO who have failed or are contraindicated to VEGF inhibitors. This recommendation was based on clinical need, acceptable clinical effectiveness compared to placebo, and the broader context of the existing listing of dexamethasone for DMO. The PBAC did not recommend extending the listing to patients with RVO who are considered 'unsuitable' for VEGF inhibitors, due to the ambiguity of the proposed restriction wording leading to potential use of an inferior and more harmful therapy than a VEGF inhibitor, based primarily on convenience. The clinical need for an alternative therapy for patients who may respond to a VEGF inhibitor, but for whom monthly injections may be difficult, was not adequately supported to make available a sub-optimal therapy for a generally short-term condition.

7.2 The PBAC recommended an Authority Required (in writing) listing for initiation of treatment and an Authority Required (telephone) listing for continuing treatment.

7.3 The PBAC noted the ESC concerns regarding the lack of definition of 'contraindicated to' and 'failed prior treatment with' VEGF inhibitors in the proposed PBS restriction. However, the PBAC considered that there was a small but identifiable population with RVO for whom these subgroups represented a clinical need and agreed with the proposed wording for the restriction for these two subgroups, consistent with the current DMO listing. The PBAC also noted that appropriate coordination was in place to amend the MBS item for the codependent technology of OCT.

7.4 For the 'unsuitable' for VEGF inhibitor subgroup in the proposed PBS restriction, the PBAC did not consider the residual unmet clinical need in RVO was analogous with that in DMO, based on the likely differences in frequency of administrations and duration of therapy. Whilst acknowledging that, as highlighted in the hearing and the consumer comments, there will be a small group of patients with RVO who will require long-term therapy, for a majority of patients only short-term therapy would be required. No evidence to support the requirement for long-term therapy in RVO was provided in the submission. The PBAC was concerned that there is greater potential for sub-optimal therapy with dexamethasone being prescribed under the 'unsuitable' criterion because it is more desirable to both the patient and the provider for non-therapeutic reasons to have less frequent administrations. The PBAC considered that, for the residual small group of patients unable to persist with long-term therapy with a VEGF inhibitor for whom the switch to dexamethasone may be a preferable clinical option, this could not be adequately managed via the proposed listing.

7.5 The PBAC noted the potential increased risk of cataracts with repeated use of

dexamethasone implant. The PBAC also noted the sponsor and consumer arguments for differentiating the RVO listing from the DMO listing and proposing not to specify that patients must have had or being scheduled to have cataract surgery, which to an extent rely on the likely short-term use of dexamethasone in RVO. The PBAC considered that this short-term use was likely to represent the majority of dexamethasone use in RVO and, without further evidence to support listing in only a pseudophakic subgroup, the listings for patients with RVO who are contraindicated to or have failed prior treatment with VEGF inhibitors would not need to refer to cataract surgery.

7.6 The PBAC agreed with the nominated comparator of sham injection, or no treatment, for patients who have failed or are contraindicated to VEGF inhibitors. The PBAC noted that the nominated comparator of VEGF inhibitor the subgroup 'unsuitable' for VEGF inhibitor would position dexamethasone implant in the south-west quadrant (ie a clinically inferior therapy offered at a lower cost).

7.7 The PBAC noted that, in the placebo-controlled trials (GENEVA 008, GENEVA 009, Trial 020), treatment response was defined as 15 or more letters improvement from baseline BCVA. The improvements in the dexamethasone implant group were statistically significant compared to placebo until 3 months. For the secondary outcome of mean change in BCVA from baseline, the greatest change was measured at month 2, where the difference between treatment groups ranged from 6.4 to 8.9 letters. The PBAC considered this difference would provide a modest benefit for some patients, with the efficacy of the dexamethasone implant waning beyond month 3. The PBAC noted the evidence from the non-randomised studies examining the effectiveness of dexamethasone implant in patients who had previously failed treatment with VEGF inhibitors was not conclusive.

7.8 The PBAC noted the inferior safety of dexamethasone versus placebo, with the increased risk of IOP, conjunctival haemorrhage, cataract and ocular hypertension.

7.9 The PBAC noted the clinical comparison of dexamethasone implant and ranibizumab (trial data from COMO, COMRADE-B, COMRADE-C) demonstrated the inferior effectiveness and safety of dexamethasone.

7.10 The PBAC noted the ESC concerns regarding the approach to the cost analysis in the submission. The PBAC also noted the pre-PBAC response (p3) which highlighted that BCVA outcomes for dexamethasone implant versus sham were similar over 6 months in patients with RVO compared with DMO, and therefore the cost-effectiveness would be no worse in RVO than in DMO. The PBAC noted the ESC remained concerned about the frequency of administrations and duration of therapy, however, considered the submission's claim may still be acceptable given the duration of therapy is likely to be less than with DMO, based on the differences in the disease trajectory. Overall, the PBAC considered the proposed cost of dexamethasone implant for RVO would be acceptable for the patients who have failed or are contraindicated to VEGF inhibitor therapy.

7.11 The PBAC agreed with the DUSC advice that the projected savings from substitution with VEGF inhibitors was unlikely to be achieved, especially given the committee's decision not to recommend dexamethasone implant for patients with RVO considered 'unsuitable' for VEGF inhibitor therapy. The PBAC agreed with DUSC that the addition of dexamethasone as a second-line therapy would result in an additional spend rather than a savings, especially given that there should be no VEGF inhibitor offsets. The market share approach used in the submission did not allow for estimation of the subgroups who have failed or are contraindicated to VEGF inhibitors. The PBAC considered the expenditure on dexamethasone for these subgroups would need to be further negotiated with the sponsor and the Department before PBS listing, and advised that the expenditure on dexamethasone implant itself would be substantially less than that estimated by the submission.

7.12 The PBAC considered that revised expenditure caps should be negotiated, with similar rebate arrangements as currently exist for DMO, but taking into account issues raised above to more appropriately restrict the RVO population. Although not a matter for the Committee, the PBAC noted that the proposed risk share arrangement in the pre-PBAC response [redacted].

7.13 The PBAC advised that dexamethasone intravitreal injection 700 micrograms is not suitable for prescribing by nurse practitioners.

7.14 The PBAC recommended that the Early Supply Rule should apply.

7.15 The re-submission is not eligible for an Independent Review, because the PBAC made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
DEXAMETHASONE INTRAVITREAL IMPLANT, 700 microgram	1	1	Ozurdex®	Allergan

PBS indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing ☐Authority Required - Telephone
Treatment criteria:	Patient must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to branched retinal vein occlusion (BRVO), **AND**

	Patient must have documented visual impairment defined as a best-corrected visual acuity score between 73 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/400), in the eye proposed for treatment, **AND** The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, **AND** Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; OR Patient must have failed prior treatment with VEGF inhibitors, **AND** The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. A written application must include: • a completed authority prescription form; • a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form; and • a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	Note: No increase in the maximum quantity or number of units may be authorised. Note: No increase in the maximum number of repeats may be authorised.
	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
	The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.

PBS indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Continuing treatment
Restriction:	☐Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	Patient must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	Patient must have previously been treated with this drug for this condition. AND The treatment must be the sole PBS-subsidised therapy for this condition.
Administrative advice	Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

PBS indication:	Central retinal vein occlusion with macular oedema

Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing ☐Authority Required - Telephone
Treatment criteria:	Patient must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), **AND** Patient must have documented visual impairment defined as a best-corrected visual acuity score between 73 and 24 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/320), in the eye proposed for treatment, **AND** The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, **AND** Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; OR Patient must have failed prior treatment with VEGF inhibitors, **AND** The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. A written application must include: • a completed authority prescription form; • a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form; and • a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Retinal Vein Occlusion Initial PBS authority application Supporting information form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	Note: No increase in the maximum quantity or number of units may be authorised. Note: No increase in the maximum number of repeats may be authorised.
	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
	The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.

PBS indication:	Central retinal vein occlusion with macular oedema
Treatment phase:	Continuing treatment
Restriction:	☐Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	Patient must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	Patient must have previously been treated with this drug for this condition.

	AND The treatment must be the sole PBS-subsidised therapy for this condition.
Administrative advice	Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.