

6.06 RANIBIZUMAB

**Solution for intravitreal injection 2.3 mg in 0.23 mL,
Solution for intravitreal injection 1.65 mg in 0.165 mL
single use pre-filled syringe,
Lucentis[®],
Novartis Pharmaceuticals Australia Pty Limited.**

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 85 (General Schedule), Authority Required (written/online) PBS listing for the initial treatment phase of ranibizumab for the treatment of proliferative diabetic retinopathy (PDR) without diabetic macular oedema (DMO), and an Authority Required (streamlined) listing for the continuing treatment phase.
- 1.2 The PBS listing was requested on the basis of a cost-utility analysis (CUA) of ranibizumab versus panretinal laser photocoagulation (PRP). The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: The key components of the clinical issue addressed in the submission

| Component | Description |
|----------------|---|
| Population | Adult patients with PDR without DMO. |
| Intervention | Ranibizumab 0.5 mg intravitreal injection once per month until maximum visual acuity is achieved and/or there are no signs of disease activity*. |
| Comparator | Panretinal laser photocoagulation. After an initial PRP session, if stability of morphological parameters was not observed after 2 months, additional PRP was allowed (PRIDE). |
| Outcomes | Improvement in visual acuity and prevention of clinically significant DMO. |
| Clinical claim | The submission claimed that in patients with PDR without DMO, ranibizumab is more effective than PRP in improving visual acuity and reducing the risk of clinically significant DMO, being non-inferior in terms of safety. |

Source: Table1.1, p3 of the submission.

DMO = diabetic macular oedema, PDR = proliferative diabetic retinopathy, PRP = Panretinal laser photocoagulation

*a minimum of three months' worth of injection to be administered to the patient before further treatment can be deferred due to stabilisation of morphological parameters

2 Background

Registration status

- 2.1 Ranibizumab was TGA registered on 2 April 2020 for adults in the following indication:
- Treatment of proliferative diabetic retinopathy.
- 2.2 Ranibizumab is also TGA registered for adults in the following conditions:
- Treatment of neovascular (wet) age-related macular degeneration.

Public Summary Document – May 2025 PBAC Meeting

- Treatment of visual impairment due to diabetic macular oedema.
 - Treatment of visual impairment due to choroidal neovascularisation.
 - Treatment of visual impairment due to macular oedema secondary to retinal vein occlusion
 - Indicated in preterm infants for the treatment of retinopathy of prematurity with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or aggressive posterior retinopathy of prematurity disease.
- 2.3 Two biosimilars (BYOOVIZ™, ARTG ID 375304, ARTG date 24 August 2022; RANIVIZ®, ARTG ID 400126, ARTG date 20 December 2023) are TGA-registered.

Previous PBAC consideration

- 2.4 The Pharmaceutical Benefits Advisory Committee (PBAC) has not previously considered ranibizumab for this indication.
- 2.5 The PBAC had previously considered this medicine for other conditions. At the July 2014 PBAC meeting the PBAC recommended ranibizumab for the treatment of visual impairment due to DMO. The PBAC stated its view on ranibizumab comparative benefits and harms remained unchanged from those in November 2013, where the submission described ranibizumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over laser photocoagulation (Ranibizumab Public Summary Document [PSD] November 2013, Ranibizumab PSD July 2014 PBAC Meeting). Ranibizumab was PBS listed July 2015 for the treatment of DMO.
- 2.6 In previous considerations for ranibizumab and of relevance to the proposed population, the PBAC noted:
- Minimal Clinical Important Difference (MCID) for Best Corrected Visual Acuity (BCVA): In November 2013, the PBAC remained concerned about the clinical importance of a 5–6 letter improvement in BCVA in the treated eye. The PBAC recalled its finding in its consideration of the March 2013 submission that ‘an increase in 5 letters or more might represent a clinically meaningful difference for some patients in the treatment of DMO’. The PBAC further clarified that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye will depend on the baseline visual acuity of the patient in both eyes and on the subsequent overall visual acuity during and after treatment. Those patients with well-preserved vision at baseline may experience a less clinically meaningful outcome than those patients with poorer vision at baseline (Ranibizumab, PSD, November 2013 PBAC meeting, p4).
 - Cost-effectiveness: In July 2014, the PBAC considered ranibizumab would be cost-effective at a reduced price that produced an ICER of between \$15,000 and \$45,000/QALY, similar to that previously accepted ICER for ranibizumab in the

Public Summary Document – May 2025 PBAC Meeting

treatment of Age-related Macular Degeneration (paragraph 6.24, ranibizumab, PSD, July 2014 PBAC meeting).

3 Requested listing

Table 2: Essential elements of the requested listing

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price Max Qty (DPMQ) | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---------------------------------------|----------------|----------------|-----------|------------------|
| RANIBIZUMAB | | | | | |
| Ranibizumab 1.65 mg/0.165 mL injection, 0.165 mL syringe | Published: \$786.36 Effective: \$■ | 1 | 1 | 2 | Lucentis |
| Ranibizumab 1.65 mg/0.165 mL injection, 0.165 mL syringe | | 1 | 1 | 5 | |
| Ranibizumab, solution for intravitreal injection 2.3 mg in 0.23 mL vial | | 1 | 1 | 2 | |
| Ranibizumab, solution for intravitreal injection 2.3 mg in 0.23 mL vial | | 1 | 1 | 5 | |

Source: Table 1.10, p.21 of the submission.

DPMQ = dispensed price for maximum quantity.

Notes: the published DPMQ was added during the evaluation (italics) based on DPMQ values in the financials calculation workbook (Attachment 7 of submission).

Table 3: Proposed PBS restriction for initial treatment with ranibizumab

| |
|--|
| Category/Program: General Schedule (Code GE) |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload |
| Indication: Proliferative diabetic retinopathy without diabetic macular oedema |
| Treatment Phase: Initial treatment |
| Clinical criteria: |
| Patient must have proliferative diabetic retinopathy |
| AND |
| Patient must not have clinically significant macular oedema secondary to diabetic retinopathy |
| AND |
| The condition must be diagnosed by fluorescein angiography |
| AND |
| The treatment must be the sole PBS-subsidised therapy for this condition |
| Treatment criteria: |
| Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist |

Source: Table 1.11, pp.22-3 of the submission.

HPOS = Health Professional Online Services, PBS = Pharmaceutical Benefits Scheme.

Public Summary Document – May 2025 PBAC Meeting

Table 4: Proposed PBS restriction for continuing treatment with ranibizumab

| |
|---|
| Category/Program: General Schedule (Code GE) |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) |
| Indication: Proliferative diabetic retinopathy without diabetic macular oedema |
| Treatment Phase: Continuing treatment |
| Clinical criteria: |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye |
| AND |
| Patient must not have developed clinically significant macular oedema secondary to diabetic retinopathy |
| AND |
| The treatment must be the sole PBS-subsidised therapy for this condition |

Source: Table 1.12, p.23 of the submission.

PBS = Pharmaceutical Benefits Scheme.

Table 5: Proposed grandfathering PBS restriction for ranibizumab

| |
|---|
| Category/Program: General Schedule (Code GE) |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) |
| Indication: Proliferative diabetic retinopathy without diabetic macular oedema |
| Treatment Phase: Initial treatment |
| Clinical criteria: |
| Patient must have had proliferative diabetic retinopathy at the time of initiating non-PBS-subsidised treatment |
| AND |
| Patient must not have clinically significant macular oedema secondary to diabetic retinopathy |
| AND |
| The condition must have been diagnosed by fluorescein angiography at the time of initiating non-PBS-subsidised treatment |
| AND |
| The treatment must be the sole PBS-subsidised therapy for this condition |
| Treatment criteria: |
| Must have been treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist at the time of initiating non-PBS-subsidised treatment |

Source: Table 1.13, p.24 of the submission.

PBS = Pharmaceutical Benefits Scheme.

- 3.1 The requested published dispensed price for maximum quantity (DPMQ) for ranibizumab of \$786.36 was consistent across all currently PBS listed conditions.
- 3.2 The submission proposed a special pricing arrangement. The initial requested effective approved ex-manufacturer price (AEMP) price of \$| was higher than the current ranibizumab effective AEMP price of \$| for the PBS listing for patients with visual impairment due to DMO, and the treatment of patients with retinal vein occlusion due to macular oedema. It is also higher than the current effective AEMP price of \$| for the PBS listing of visual impairment due to subfoveal choroidal neovascularisation due to rare causes and secondary pathologic myopia. A price reduction, equivalent to the current effective AEMP for patients with visual impairment due to DMO (AEMP \$|) was proposed by the sponsor as part of the pre-PBAC response.

Public Summary Document – May 2025 PBAC Meeting

- 3.3 The requested PBS listing was narrower than the current TGA indication as it was restricted to include only patients with PDR without DMO. Patients with visual impairment due to DMO can currently access ranibizumab via the PBS (item number 10373Y, 13165X, 10374B, 13134G). The Drug Utilisation Sub-Committee (DUSC) noted the proposed restriction may lead to a treatment gap, where a patient who received ranibizumab for PDR without DMO subsequently progressed to PDR with DMO and the patient did not qualify for PBS-reimbursed access based on the vision impairment requirement. The DUSC considered that the restriction's exclusion criteria could be modified from 'Patient must not have clinically significant macular oedema secondary to diabetic retinopathy' to 'Patient is not being treated with or does not qualify for, PBS subsidised treatment for macular oedema secondary to diabetic retinopathy'. The Pre-PBAC Response noted the sponsor was willing to accept the expanded indication.
- 3.4 The submission proposed restriction was based on the PBS listing for DMO, with the notable exclusion of associated criterion requiring patients to demonstrate visual impairment prior to treatment, as well as diagnosis of the condition through Optical Coherence Tomography (OCT) (although reference to OCT was retained in the prescribing instructions). The DUSC considered the proposed requirement of fluorescein angiography for diagnosis of PDR to be invasive and unnecessary.
- 3.5 A grandfathering restriction was requested for the 500 to <5,000 PDR patients enrolled in a ranibizumab compassionate access scheme. The secretariat proposed restriction wording that combined the initial and grandfather treatment phases into one generalised listing. The evaluation noted, the sponsor commenced a compassionate access scheme for patients with PDR in 2018 and stated it would not be able to continue once biosimilars were available. Given the significant number of patients enrolled in the scheme, the ESC considered it pertinent to know characteristics of the patients currently accessing ranibizumab, including details of age, how many patients identify as Aboriginal and Torres Strait Islander people, duration of therapy and clarification of the conditions for which access was provided. The Pre-PBAC response stated baseline patient characteristics and follow-up data was not collected due to privacy restraints and as the scheme was not designed as a real-world evidence study, no further data could be provided.

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

4 Population and disease

- 4.1 PDR is an advanced stage of diabetic retinopathy (DR), a common microvascular complication in patients with type I and type II diabetes. PDR is characterised by abnormal neovascularisation, which is triggered by the release of vascular endothelial growth factor (VEGF) in response to sustained retinal hypoxia, eventually resulting in vision impairment and blindness. Without appropriate intervention, approximately

Public Summary Document – May 2025 PBAC Meeting

half of all patients with high-risk PDR will experience visual impairments due to DMO, vitreous haemorrhage, and/or retinal detachment within 5 years of diagnosis¹.

- 4.2 DMO is a vision-threatening complication of DR. The risk of developing DMO is significantly higher for patients with PDR than for those with mild to severe non-proliferative diabetic retinopathy (NPDR).
- 4.3 Vision impairment due to DR is often irreversible and has significant impact on patient quality of life (QoL). The submission highlighted the need for effective interventions to prevent vision loss due to DMO and improve patient outcomes.
- 4.4 The burden of disease is also disproportionately high among Aboriginal and Torres Strait Islander people, who experience significantly higher rates of diabetes-related complications and severe and vision-threatening PDR, compared to non-Indigenous Australians.
- 4.5 Anti-VEGF therapies, including aflibercept, faricimab and ranibizumab, as well as dexamethasone implants, were PBS listed treatments for patients with visual impairment due to DMO. Patients with PDR must develop vision impairment due to DMO before they can access PBS-subsidised treatments.
- 4.6 Panretinal laser photocoagulation was the current standard of care for reducing the risk of vision loss in PDR.
- 4.7 The target population in this submission adult patients with PDR classified by the Early Treatment of Diabetic Retinopathy Study (ETDRS) modified Airlie House Diabetic Retinopathy Severity Scale (DRSS), without DMO.
- 4.8 Ranibizumab, a humanised recombinant monoclonal antibody fragment, targets all active isoforms of VEGF-A to inhibit endothelial cell proliferation, neovascularisation and vascular leakage, which are key factors in the progression of diabetic retinopathy.
- 4.9 The goal of, and underlying pathophysiological mechanism of, ranibizumab is to reduce neovascularisation (NV) and to reduce the risk of progression to DMO.
- 4.10 Neovascularisation is the key driver of PDR and is triggered by VEGF binding to its receptors. In order to meet the high metabolic requirement of the retina, new blood vessels develop. However, these blood vessels are malformed and fragile potentially leaking blood into the retina and vitreous, this fluid accumulation is known as DMO, which can lead to retinal detachment and vision loss.

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

¹ Singh R.P. et al 'Advances in the treatment of diabetic retinopathy', [Journal of Diabetes and its Complications](#), Volume 33, Issue 12, December 2019

5 Comparator

- 5.1 The nominated comparator in the submission was laser photocoagulation, specifically panretinal laser photocoagulation (PRP), which has been the standard treatment for PDR patients without DMO. The ESC considered this was reasonable, as there were no PBS-listed treatments for PDR or alternate anti-VEGF with a similar approved TGA indication.
- 5.2 Ranibizumab was proposed as an alternative first-line treatment option for patients with PDR. The ESC and DUSC considered a patient may be treated with ranibizumab prior to or subsequent to PRP treatment, where the use of ranibizumab may be guided by clinical assessment and/or individual patient preference.
- 5.3 The PBAC previously accepted laser photocoagulation as an appropriate comparator to ranibizumab in their recommendation for PBS listing of visual impairment due to DMO at the July 2014 PBAC meeting (para 7.3, Ranibizumab PSD, July 2014 PBAC Meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from 4 health professionals working in the area and 1 organisation. The health care professionals described PDR as the most common cause of blindness in working-age individuals in Australia. The input noted that current therapy with PRP may result in loss of peripheral vision and is not suitable for those presenting with vitreous haemorrhage and advanced cataracts. It was noted ranibizumab improved visual outcomes, was valuable in stopping further bleeding whilst laser (PRP) can be carried out, and improving the laser uptake as the retina becomes less oedematous overall. It was further noted ranibizumab, delivered via intra-vitreous injection, is less invasive and has fewer risks than vitrectomy surgery, which can result in cataracts. This was considered important given the inequity of vitrectomy surgery not being available in all regional settings, often not available in a general practice setting and the waitlist in the public surgery can result in the worsening of vitreous haemorrhage. It was also noted there is a time and cost burden to monthly treatment with ranibizumab, although it is expected once PDR is under control, treatment requirements become less frequent (3–4 months), and those undergoing treatment do not find this onerous.
- 6.3 Macular Disease Foundation Australia (MDFA) noted Aboriginal and Torres Strait Islander people are at increased risk of vision loss from diabetic eye disease, noting at

Public Summary Document – May 2025 PBAC Meeting

least four times more likely than non-indigenous Australians to develop diabetes. It was further noted that vision loss due to diabetic retinopathy results in higher rates of unemployment and underemployment, reduced safety in the workplace and home, increased rates of depression and greater dependence on carers. MDFA supported a PBS listing for ranibizumab and noted some ophthalmologists might consider using the therapy in combination with PRP, or alone as alternative therapy.

Clinical trials

6.4 The submission was based on 2 head-to-head randomised trials comparing ranibizumab to PRP: the PRIDE trial and the Protocol S trial. Two additional trials were identified in the literature search comparing ranibizumab to PRP that were excluded, due to low number of participants (n=35) and short duration of follow-up (3 months).

6.5 Details of the trials presented in the submission are provided in Table 6.

Table 6: Trials and associated reports presented in the submission

| Trial ID | Protocol/Publication title | Publication citation |
|------------------------|--|---|
| DRCR.net Protocol S | Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy. Report No. 1066857. Protocol S (Protocol ML27976) plus Investigator’s signature. | Clinical Study Report; September 2016. |
| | Gross, J. G., Glassman, A. R., Jampol, L. M., Inusah, S., Aiello, L. P., Antoszyk, A. N., Baker, C. W., Berger, B. B., Bressler, N. M., Browning, D., Elman, M. J., Ferris, F. L., Friedman, S. M., Marcus, D. M., Melia, M., Stockdale, C. R., Sun, J. K., & Beck, R. W. (2015). Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial. | Full publication; JAMA – Journal of the American Medical Association, 314(20), 2137-2146. https://doi.org/10.1001/jama.2015.15217 |
| | Gross, J. G., Glassman, A. R., Liu, D., Sun, J. K., Antoszyk, A. N., Baker, C. W., Bressler, N. M., Elman, M. J., Ferris, F. L., Gardner, T. W., & et al (2018). Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy: a Randomized Clinical Trial. | Full publication; JAMA Ophthalmology, 136(10), 1138-1148. https://doi.org/10.1001/jamaophthalmol.2018.3255 |
| | Beaulieu, W. T., Bressler, N. M., Melia, M., Owsley, C., Mein, C. E., Gross, J. G., Jampol, L. M., & Glassman, A. R. (2016). Panretinal Photocoagulation Versus Ranibizumab for Proliferative Diabetic Retinopathy: Patient-Centered Outcomes From a Randomized Clinical Trial. | Full publication; American Journal of Ophthalmology, 170, i. https://doi.org/10.1016/j.ajo.2016.08.008 |
| | Bressler, S. B., Beaulieu, W. T., Glassman, A. R., Gross, J. G., Jampol, L. M., Melia, M., Peters, M. A., & Rauser, M. E. (2017). Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab. Bressler, S. B., Beaulieu, W. T., Glassman, A. R., Gross, J. G., Melia, M., Chen, E., Pavlica, M. R., & Jampol, L. M. (2018). Panretinal Photocoagulation Versus Ranibizumab for Proliferative Diabetic Retinopathy: Factors Associated with Vision and Edema Outcomes. | Full publication; Ophthalmology, 124(4), 431-439. https://doi.org/10.1016/j.ophtha.2016.12.005 Full publication; Ophthalmology, 125(11), 1776-1783. https://doi.org/10.1016/j.ophtha.2018.04.039 |

Public Summary Document – May 2025 PBAC Meeting

| Trial ID | Protocol/Publication title | Publication citation |
|----------|--|---|
| | <p>Bressler, S. B., Beaulieu, W. T., Glassman, A. R., Gross, J. G., Melia, M., Chen, E., Pavlica, M. R., & Jampol, L. M. (2019). Photocoagulation versus ranibizumab for proliferative diabetic retinopathy: Should Baseline Characteristics Affect Choice of Treatment?</p> <p>Jampol, L. M., Odia, I., Glassman, A. R., Baker, C. W., Bhorade, A. M., Han, D. P., Jaffe, G. J., Melia, M., Bressler, N. M., & Tanna, A. P. (2019). Panretinal photocoagulation versus ranibizumab for proliferative diabetic retinopathy: Comparison of peripapillary retinal nerve fiber layer thickness in a randomized clinical trial.</p> <p>Maguire, M. G., Liu, D., Glassman, A. R., Jampol, L. M., Johnson, C. A., Baker, C. W., Bressler, N. M., Gardner, T. W., Pieramici, D., Stockdale, C. R., & Sun, J. K. (2020). Visual Field Changes over 5 Years in Patients Treated with Panretinal Photocoagulation or Ranibizumab for Proliferative Diabetic Retinopathy.</p> | <p>Full publication; Retina, 39(9), 1646-1654. https://doi.org/10.1097/IAE.0000000000002377</p> <p>Full publication; Retina, 39(1), 69-78. https://doi.org/10.1097/IAE.0000000000001909</p> <p>Full publication; JAMA Ophthalmology, 138(3), 285-293. https://doi.org/10.1001/jamaophthalmol.2019.5939</p> |
| | <p>Sun, J. K., Glassman, A. R., Beaulieu, W. T., Stockdale, C. R., Bressler, N. M., Flaxel, C., Gross, J. G., Shami, M., & Jampol, L. M. (2019). Rationale and Application of the Protocol S Anti-Vascular Endothelial Growth Factor Algorithm for Proliferative Diabetic Retinopathy.</p> | <p>Full publication; Ophthalmology, 126(1), 87-95. https://doi.org/10.1016/j.ophtha.2018.08.001</p> |
| | <p>Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy.</p> <p>Nct. (2011). Prompt Panretinal Photocoagulation Versus Ranibizumab+Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy.</p> | <p>Trial registry record; 2011; https://clinicaltrials.gov/study/NCT01489189</p> <p>Trial registry record; 2011; https://clinicaltrials.gov/show/NCT01489189. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02046877/full</p> |
| PRIDE | <p>Multicenter randomized open-label three-arms controlled 12 months clinical proof of concept study to evaluate efficacy and safety of Ranibizumab alone or in combination with laser photocoagulation vs laser photocoagulation alone in Proliferative Diabetic Retinopathy. CRFB002DDE21 plus Patient Tables and Amendment 1.</p> <p>Lang, G. E., Stahl, A., Voegeler, J., Quiering, C., Lorenz, K., Spital, G., & Liakopoulos, S. (2020). Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy – the PRIDE study.</p> <p>Lang, G. E., Stahl, A., Voegeler, J., Quiering, C., Zaremba, L., Lorenz, K., Spital, G., & Liakopoulos, S. (2022). Observational outcomes in proliferative diabetic retinopathy patients following treatment with ranibizumab, panretinal laser photocoagulation or combination therapy – The non-interventional second year follow-up to the PRIDE study.</p> <p>Multicenter Randomized Open-label Three-arms Controlled 12 Months Clinical Proof of Concept Study to Evaluate Efficacy and Safety of Ranibizumab Alone or in Combination With Laser Photocoagulation vs Laser Photocoagulation Alone in Proliferative Diabetic Retinopathy.</p> | <p>Clinical Study Report</p> <p>Full publication; Acta Ophthalmologica, 98(5), e530-e539. https://doi.org/10.1111/aos.14312</p> <p>Full publication; Acta Ophthalmologica, 100(2), e578-e587. https://doi.org/10.1111/aos.14907</p> <p>Trial registry record; 2012; https://clinicaltrials.gov/study/NCT01594281</p> |

Public Summary Document – May 2025 PBAC Meeting

| Trial ID | Protocol/Publication title | Publication citation |
|----------|---|--|
| | Nct. (2012). Multicenter 12 Months Clinical Study to Evaluate Efficacy and Safety of Ranibizumab Alone or in Combination With Laser Photocoagulation vs Laser Photocoagulation Alone in Proliferative Diabetic Retinopathy (PRIDE). | Trial registry record; 2012; https://clinicaltrials.gov/show/NCT01594281 . https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01503319/full |

Source: Table 2.5, pg. 71-73 of the submission.

6.6 The key features of the trials are summarised in Table 7.

Table 7: Key features of the included evidence

| Trial | N | Design/duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|---------------------------|--------------------|--|------------------------------------|--|--|
| Ranibizumab vs panretinal photocoagulation | | | | | | |
| Protocol S | 394 eyes; 305 patients | R, MC 24 mo | Moderate | Patients with PDR with/without DMO | Primary: mean change in BCVA Secondary: proportion of eyes developing DMO, proportion with BCVA gain or loss $\geq 10/15$ letters | Transition probabilities: Proportion of patients with a 10- or 15-letter change in BCVA) The annual probability of developing DMO was informed by 5-year follow-up |
| PRIDE | 106 patients | R, OL, MC 12 mo | Primary period = low Observational period = high ^a | Patients with PDR without DMO | Primary: mean change in area of NV Secondary: mean change in BCVA, proportion with BCVA gain or loss $\geq 5/10/15$ letters | Demographic characteristics: Age 53.5 years Male proportion 68.90% Transition probabilities: Proportion of patients with a 5-letter change in BCVA |

Source: Compiled during the evaluation.

BCVA = best corrected visual acuity, DMO = diabetic macular oedema, MC = multicentre, mo = months, NV = neovascularisation, OL = open label, R = randomised.

^a RoB was assessed individually in PRIDE for the primary 12-month study period and the observational 12-month study period.

6.7 The evaluation assessed the overall risk of bias (RoB) for Protocol S to be of moderate risk. The overall RoB for PRIDE during the primary analysis period was assessed to be of low risk, whereas the observational period of PRIDE was assessed to be of high risk. The domain-specific RoB was not reported, this makes it difficult to decipher which domains were assessed as being of some concern or high RoB in the included trials.

6.8 Neither the safety nor efficacy analyses were meta-analysed. The reasoning provided in the submission was that the evidence base would be confounded by the Protocol S trial population including PDR patients with DMO. PRIDE published separate results for the two phases (i.e. interventional and observational). Protocol S presented stratified results between PDR patients with and without DMO at baseline, for both the 2- and 5-year timepoints. Therefore, the evaluation noted meta-analyses may be possible using the data from the interventional phase of the PRIDE trial and the Protocol S subgroup of PDR patients without DMO at baseline.

6.9 The Protocol S trial included 305 patients (394 eyes) with PDR with or without DMO over a 60-month period, assessing changes in BCVA, visual acuity of $\geq 10/15$ letters

Public Summary Document – May 2025 PBAC Meeting

gains or loss, and the risk of developing DMO. In contrast, the PRIDE trial focused specifically on 106 patients with PDR without DMO over 24 months, measuring BCVA, changes in NV, and visual acuity of $\geq 5/10/15$ letters gains or loss. In Protocol S, 191 eyes were allocated randomly to ranibizumab, and 204 to PRP. Contrastingly, in the PRIDE trial, at randomisation 35 patients were allocated ranibizumab, 35 patients to PRP, and 36 patients to the combined treatment of ranibizumab and PRP. The evaluation only reported the outcomes of the ranibizumab and PRP monotherapy arms of the PRIDE trial.

- 6.10 Treatment effects from the clinical evidence were affected by treatment switching. After 2 years of follow-up in the Protocol S trial, over 50% of patients within the laser arm had received ranibizumab. Within the PRIDE trial, randomisation was maintained and patients switched from PRP to ranibizumab if they developed DMO. The second year of the PRIDE trial was observational and patients switched between ranibizumab and PRP at the discretion of the lead investigator. The ESC noted the total population in Protocol S included a subset of patients that had DMO at baseline, a broader population than the requested PBS listing. The ESC further noted both Protocol S and PRIDE included high rates of cross over from PRP to ranibizumab which created uncertainty with respect to the clinical effectiveness for patients treated with ranibizumab for PDR without DMO compared to PRP.

Comparative effectiveness

- 6.11 The BCVA outcomes are presented in Table 8. The PRIDE trial reported an adjusted mean difference (MD) of 5.5 letters in favour of ranibizumab at the 1-year timepoint. At the 2-year timepoint Protocol S reported an MD of 3.5 letters in favour of ranibizumab. However, at the 5-year timepoint, Protocol S reported a MD of 0.6 letters (95% CI: -2.3, 3.5) in favour of PRP.

Public Summary Document – May 2025 PBAC Meeting

Table 8: Submission results of best corrected visual acuity (letters) across trials

| Trial ID | Time-point | Ranibizumab | | | | PRP | | | | LS MD (95% CI) |
|------------------------------------|------------|-------------|--------------------|----------------------------|----------------------------|-------------|--------------------|----------------------------|--------------------|-------------------------------------|
| | | Sample size | Baseline mean (SD) | Follow-up mean (95% CI/SD) | Change in mean (95% CI/SD) | Sample size | Baseline mean (SD) | Follow-up mean (95% CI/SD) | Change in mean | |
| PRIDE | 1 year | 35 | 83.3 (7.4) | 84.1 (81.1, 87.1) | 1.6 (-2.3, 5.5) | 35 | 80.5 (8.3) | 79.90 (77.0, 82.9) | -3.90 (-7.8, -0.1) | 5.50^b (0.0, 11.0) |
| PRIDE ^a (observational) | 2 year | 28 | 83.3 (7.4) | NR | -1.1 (-6.7, 4.6) | 20 | 80.5 (8.3) | NR | -2.0 (-8.5, 4.5) | NR ^c |
| Protocol S | 2 year | 191 | 75.0 (12.8) | NR | 4.10 (1.5, 6.7) | 204 | 75.2 (12.5) | NR | 0.7 (-1.8, 3.2) | 3.50^d (0.2, 6.7) |
| Protocol S | 5 year | 117 | 77.0 (12.0) | 80.0 (16.0) | 3.1 (14.3) | 123 | 78.0 (11.0) | 81.0 (12.0) | 3.0 (10.5) | 0.60 ^{e, f} (-2.3, 3.5) |

Source: Table 2.15, p 84 of the submission.

CI = confidence interval, LS = least square, MD = mean difference, NR = not reported, PRP = panretinal photocoagulation laser, SD = standard deviation.

Bold indicates statistically significant results.

^a Observational data

^b ANCOVA model with treatment as the factor and baseline visual acuity and number of eyes enrolled as covariate. Missing values were replaced with the LOCF until EOCS.

^c p value of 0.8300 reported.

^d ANOVA model stratified for baseline DMO status and number of eyes enrolled. Estimates, CIs, means and p value is from the ANOVA t-test (stratified)

^e ANCOVA model and binomial regression for binary outcomes, with adjustment for baseline VA, laterality, baseline central subfield thickness, and correlation between 2 study eyes of the same participant, and multiple imputation for missing data unless otherwise specified. When binomial regression model failed to converge, covariates were removed from the model. Visual acuity change was truncated to 3SD from the mean (-47 to 52) to minimise the effect of outliers (5 eyes for ranibizumab, all on the negative end).

^f p = 0.47 for comparing mean change in VA letter score at 5 years between treatment groups, with additional adjustment for potential baseline confounders, including age, duration of diabetes, haemoglobin A1c level, prior treatment for diabetic macular oedema, and diabetic retinopathy severity on fundus photographs graded by the reading centre

6.12 Using the submission’s proposed MCID of 5 letters, only the 1-year timepoint reported in PRIDE was clinically meaningful.

6.13 The proposed MCID of 5 letters was based on the MCID PBAC had previously accepted for vision impaired DMO. However, the ESC noted the PBAC acceptance of this MCID also factored in patients’ baseline visual acuity (see paragraph 2.6) and the ESC considered that 10 letters was more likely to be a meaningful difference for the PDR population. DMO is a more severe condition that inherently requires a lower MCID of the number of letters, making this comparison a false equivalency. Using an inappropriately low MCID from DMO to justify clinical relevance in PDR may exaggerate the perceived clinical benefit. The Pre-Sub-Committee Response (PSCR) argued the MCID for BCVA of 5 letters was consistent with the non-inferiority margin in Protocol S and was a sensible choice to capture meaningful improvements in vision-related quality of life. However, the ESC noted that a margin set for non-inferiority does not necessarily represent a clinically meaningful difference. Regardless, the ESC noted that even if a MCID of 5 letters was considered appropriate for the PDR without DMO population, the outcome was only reached at a single time point and was largely achieved via a decrement in visual acuity for the PRP arm rather than a meaningful improvement with ranibizumab treatment.

Public Summary Document – May 2025 PBAC Meeting

- 6.14 The continual decrease in MD at each of the 1-year, 2-year, and 5-year timepoints may not be due to ranibizumab having poor durability, but by selection bias that was the result of a high amount of treatment switching between ranibizumab and PRP in the Protocol S trial.
- 6.15 The decrease in the BCVA below baseline experienced in the PRIDE and Protocol S PRP arms was not unexpected given PRP can cause peripheral retinal damage, decreasing contrast sensitivity, night vision, and overall visual field.
- 6.16 The Protocol S trial includes patients with DMO and PDR, whereas the requested PBS listing was for PDR only without DMO. A subgroup analysis was presented in the submission, however, statistical analyses of the subgroups were not available. The mean differences for each subgroup were calculated during the evaluation and stated in Table 9.

Table 9: Results of best corrected visual acuity (letters) subgroup analysis by baseline DMO status at 2 years

| Population | Trial ID | Ranibizumab | | PRP | | MD (95% CI) |
|------------------------|-------------------------|------------------|-------------|------------------|-------------|---------------------------|
| | | Mean (95% CI/SD) | Sample size | Mean (95% CI/SD) | Sample size | |
| Whole trial population | Protocol S ^a | 4.1 (1.5, 6.7) | 191 | 0.7 (-1.8, 3.2) | 203 | 3.50 (0.20, 6.70) |
| Without baseline DMO | Protocol S | 0.8 (18.4) | 149 | -1.2 (14.1) | 157 | <i>2.00 (-1.70, 5.70)</i> |
| With baseline DMO | Protocol S | 9.3 (13.6) | 42 | 1.2 (19.4) | 46 | 8.10 (1.05, 15.15) |

Source: Table 2.31, p110 of the submission.

CI = confidence interval, k = number of publications, MD = mean difference, SD = standard deviation.

^a ANOVA model stratified for baseline DMO status and number of eyes enrolled. Estimates, CIs, means and p-value is from the ANOVA t-test (stratified)

I² could not be calculated as one 1 trial was included.

Bold indicates statistically significant results.

Italics indicates statistics calculated during evaluation

- 6.17 The naive comparison of subgroup MDs indicated that the presence of baseline DMO inflates the effectiveness of ranibizumab. Due to the inclusion of patients with DMO at baseline, the Protocol S ITT data has likely overestimated the ranibizumab treatment effect.
- 6.18 A summary of visual acuity letter gain or loss ($\geq 5/10/15$) was presented in Table 10. The submission did not present the relative risk (RR) of each of the letter gains or losses reported. The RR was calculated during the evaluation.

Public Summary Document – May 2025 PBAC Meeting

Table 10: Submission results for visual acuity gain or loss (≥5/10/15 letters) across trials

| Trial ID | Timepoint | Ranibizumab | PRP | Difference in proportion (95% CI), p value | Relative Risk (95% CI) |
|-------------------------|-----------|--------------|--------------|--|--------------------------|
| ≥ 5-letter gain | | | | | |
| PRIDE | 1 year | 11/35 (31%) | 7/35 (20%) | NR | 1.57 (0.69, 3.58) |
| ≥ 10-letter gain | | | | | |
| PRIDE | 1 year | 2/35 (6%) | 4/35 (11%) | NR | 0.50 (0.10, 2.56) |
| Protocol S ^b | 2 year | 55/191 (3%) | 37/203 (19%) | 10.9% (2.9, 18.8), p<0.01 | 1.58 (1.09, 2.28) |
| Protocol S ^c | 5 year | 28/54 (52%) | 23/56 (16%) | 6% (-10.0, 21.0), p=0.47 | 1.26 (0.84, 1.89) |
| ≥ 15-letter gain | | | | | |
| PRIDE ^a | 1 year | 0/35 (0%) | 1/35 (3%) | NR | 0.50 (0.02, 14.43) |
| Protocol S ^b | 2 year | 31/191 (16%) | 22/203 (11%) | 5.6% (-0.8, 11.7), p=0.09 | 1.50 (0.90, 2.49) |
| Protocol S ^c | 5 year | 14/54 (26%) | 23/56 (41%) | 1% (-12.0, 15.0), p=0.86 | 0.63 (0.36, 1.09) |
| ≥ 5-letter loss | | | | | |
| PRIDE | 1 year | 6/35 (17%) | 13/35 (37%) | NR | 0.46 (0.20, 1.08) |
| ≥ 10-letter loss | | | | | |
| PRIDE | 1 year | 4/35 (11%) | 4/35 (11%) | NR | 1.00 (0.27, 3.69) |
| Protocol S | 2 year | 17/191 (9%) | 29/203 (14%) | NR | 0.62 (0.35, 1.10) |
| Protocol S ^c | 5 year | 7/117 (6%) | 11/123 (9%) | -3% (-11.0, 5.0), p=0.42 | 0.67 (0.27, 1.67) |
| ≥ 15-letter loss | | | | | |
| PRIDE | 1 year | 1/35 (3%) | 3/35 (9%) | NR | 1.00 (0.07, 15.36) |
| Protocol S | 2 year | 13/191 (7%) | 22/203 (11%) | NR | 0.63 (0.33, 1.21) |
| Protocol S ^c | 5 year | 7/117 (6%) | 7/123 (6%) | -1% (-7.0, 5.0), p=0.84 | 1.05 (0.38, 2.91) |

Source: Table 2.17, p 86 of submission.

CI = confidence interval, CMH = Cochran-Mantel-Haenszel, DMO = diabetic macular oedema, NA = not applicable, NR = not reported, PRP = panretinal photocoagulation laser.

Bold indicates statistically significant results.

Italics indicate statistics calculated by evaluation group

^a Odds ratios not calculated when there were zero frequencies

^b CMH χ^2 test stratified by baseline DMO status and number of study eyes enrolled. Missing values replaced with last observation carried forward (LOCF) until end of study.

^c Treatment group percentages calculated from observed data from patients who completed follow-up.

^d CMH weighted proportion.

- 6.19 No statistical differences existed between treatments for ≥5, ≥10 or ≥15 letters gained or lost at 1-, 2- and 5-year follow-up. The lack of statistically significant findings is not unexpected as PDR treatment aims to reduce NV and minimise DMO. Due to the inclusion of patients with PDR at the DMO baseline, the Protocol S data has likely overestimated the ranibizumab treatment effect.
- 6.20 Only data from Protocol S reported the risk of developing clinically significant DMO. A summary of risk of DMO is presented in Table 11.

Public Summary Document – May 2025 PBAC Meeting

Table 11: Submission results of risk of DMO across the trials

| Trial ID | Timepoint | Ranibizumab | PRP | Absolute difference | HR (95% CI) |
|---|-----------|----------------|----------------|---------------------|-----------------------------|
| Risk of clinically significant DMO | | | | | |
| Protocol S | 1 year | 9/141 (6.1%) | 37/157 (23.8%) | NR | NR ^a |
| Protocol S | 2 year | 15/141 (10.5%) | 45/157 (28.6%) | NR | NR ^a |
| Protocol S | 5 year | 31/141 (22%) | 59/157 (38%) | NR | 0.4 (0.3, 0.7) ^b |

Source: Text & Figure 2.8, p88 of the submission; Table 2.18, p89 of the submission.

CI = confidence interval, DMO = diabetic macular oedema, HR = hazard ratio, NR = not reported, PRP = panretinal photocoagulation laser. **Bold** indicates statistically significant results.

^a p-value < 0.0001 using log-rank p-value based on a two-sided stratified log-rank test with stratification variables baseline DMO status and number of study eyes enrolled.

^b p-value < 0.001 using marginal Cox proportional hazards model, with adjustment for baseline OCT CST, laterality, and correlation between 2 study eyes of the same patient.

6.21 Patients without DMO at baseline who received ranibizumab had a significantly reduced risk of developing DMO over 5-years, with a hazard ratio (HR) of 0.4 (95% CI: 0.3, 0.7), indicating a reduction in the risk of DMO development in the ranibizumab group compared to the PRP group.

6.22 A summary of neovascularisation across trials can be found in Table 12.

Table 12: Submission results for change in area of NV, NVE and NVD - mean area of NV (mm²)

| Trial ID | Time-point | Ranibizumab | | | | PRP | | | | LS MD (95% CI) |
|-----------------------|------------|-------------|--------------------|---------------------|---------------------------|-------------|--------------------|---------------------|---------------------------|---------------------------------|
| | | Sample size | Baseline mean (SD) | Follow-up mean (SD) | Change in mean (95%CI/SD) | Sample size | Baseline mean (SD) | Follow-up mean (SD) | Change in mean (95%CI/SD) | |
| NVA | | | | | | | | | | |
| PRIDE | 1 year | 35 | 9.39 (15.41) | 2.70 (4.11) | -4.6 (11.3) | 35 | 5.40 (9.68) | 4.58 (11.4) | -0.90 (3.9) | -2.8 (-5.4, -0.2) |
| PRIDE (observational) | 2 year | 28 | NR | NR | 1.0 (-3.2, 5.1) | 20 | NR | NR | -2.2 (-6.9, 2.5) | 3.20 (-3.24, 9.64) ^a |
| NVD | | | | | | | | | | |
| PRIDE | 1 year | 35 | 1.33 (4.46) | 0.42 (1.97) | -0.91 (6.90) | 35 | 0.61 (1.63) | 0.67 (2.7) | 0.06 (4.46) | -0.97 (3.74, 1.80) |
| NVE | | | | | | | | | | |
| PRIDE | 1 year | 35 | 8.06 (15.05) | 2.48 (4.08) | -5.8 (22.07) | 35 | 4.79 (9.59) | 4.33 (12.7) | -0.46 (22.51) | -5.12 (-15.75, 5.51) |

Source: Table 2.20, p91 of the submission.

CI = confidence interval, LS = least square, MD = mean difference, NR = not reported, NVA = neovascularisation of the angle, NVD = neovascularisation of the disc, NVE = neovascularisation elsewhere, PRP = panretinal photocoagulation laser, SD = standard deviation.

Bold indicates statistically significant results.

Italics indicate statistics calculated during evaluation

NVA consists of two components, NVD and NVE.

^a p value = 0.31

6.23 NV was only reported in the PRIDE trial at the 1- and 2-year timepoints. The submission reported NV of the angle (NVA), NV elsewhere (NVE) and NV of the disc (NVD).

6.24 At the 1-year timepoint, both ranibizumab and PRP minimised NV in patients with PDR. The MD of -2.8 mm² statistically significantly favours ranibizumab over to PRP. It is not possible to determine if the MD is clinically meaningful, as there is no accepted MCID for change in any type of NV measure in patients with PDR.

Public Summary Document – May 2025 PBAC Meeting

6.25 At the 2-year timepoint, the MD favoured PRP treatment over ranibizumab, however, it was not statistically significant. The results could suggest the ranibizumab treatment effect was waning. The ESC considered the results of the observational phase of the PRIDE trial need to be interpreted with caution as it was likely affected by selection bias.

Comparative harms

6.26 A summary of the safety profile of ranibizumab and PRP across trials can be found in Table 13 and Table 14.

6.27 The safety profile of ranibizumab and PRP appeared to be consistent across both trials. The submission did not report any statistical testing to compare adverse event (AE) rates between treatments.

6.28 In the PRIDE trial ocular treatment-emergent AEs (TEAE) were more frequent in the ranibizumab group compared to the laser group. The submission reported that TEAEs were mainly due to injection-related effects, rather than the ranibizumab itself. Non-ocular TEAEs were also common in both treatment groups but were more common in ranibizumab patients. Serious AEs (SAE) were slightly higher in the ranibizumab group.

6.29 Protocol S, on the other hand, reported similar rates of ocular AEs regardless of treatment group. SAEs were rare in Protocol S regardless of treatment group. Non-ocular AEs were consistent across treatment groups. No deaths were attributed to ranibizumab over both the 2- and 5-year timepoints.

Table 13: Submission results of key adverse events in the trials

| Trial ID | Type of AE | Timepoint | Ranibizumab | PRP |
|-----------------------|------------|-----------|-----------------|-----------------|
| Ocular | | | | |
| PRIDE | TEAE | 1 year | 32/35 (91.4%) | 27/35 (77.1%) |
| PRIDE (observational) | TEAE | 1 year | 18/28 (64.3%) | 12/20 (60.0%) |
| Protocol S | Total AE | 2 year | 152/191 (79.6%) | 164/203 (80.8%) |
| PRIDE | SAE | 1 year | 2/35 (5.7%) | 2/35 (5.7%) |
| PRIDE (observational) | SAE | 1 year | 1/28 (3.6%) | 0/20 (0.0%) |
| Protocol S | SAE | 2 year | 3/191 (1.6%) | 2/203 (1%) |
| Non-ocular | | | | |
| PRIDE | Total AE | 1 year | 29/35 (82.9%) | 25/35 (71.4%) |
| PRIDE (observational) | Total AE | 1 year | 17/28 (60.7%) | 10/20 (50.0%) |
| Protocol S | Total AE | 2 year | 92/102 (90.2%) | 91/114 (79.8%) |
| PRIDE | SAE | 1 year | 5/35 (14.3%) | 3/35 (8.6%) |
| PRIDE (observational) | SAE | 1 year | 4/28 (14.3%) | 3/20 (15.0%) |
| Protocol S | SAE | 2 year | 49/102 (48.0%) | 42/114 (36.8%) |

Source: Table 2.21, p 94 of the submission; Table 2.22, p95 of the submission; Table 2.25 p101 of the submission; Table 2.26. p102 of the submission; Table 2.29, p 107 of the submission.

AE = adverse event, CI = confidence interval, IOP = intraocular pressure, NR = not reported, PRP = panretinal photocoagulation laser, RR = relative risk, SAE = serious adverse event, TEAE = treatment-emergent adverse event

6.30 In Protocol S, the rate of developing a complication requiring vitrectomy was halved in patient eyes that received ranibizumab compared to laser over five years (cumulative probabilities 15% vs 22%, HR 0.5 [95% CI: 0.3-0.8], p=0.008). The

Public Summary Document – May 2025 PBAC Meeting

submission identified this as of particular importance for Aboriginal and Torres Strait Islander people, as reducing the number of patients who require vitrectomy due to PDR meant resources in health services could be redirected to decrease the load and wait times for other procedures such as cataract surgery. Upon reviewing PRIDE and Protocol S publications, the evaluation identified further data on numbers of vitrectomies during the randomised phases of both trials, presented in Table 14 below. The ESC noted the reduction in vitrectomies may lead to a significant decrease in the surgical procedures needed to treat this serious and complex complication.

Table 14: Vitrectomy results in the trials

| Trial ID | Type of AE | Timepoint | Ranibizumab | PRP | RR (95% CI) |
|---------------|-------------------------|-----------|-------------|--------------|--------------------------|
| Ocular | | | | | |
| PRIDE | Vitrectomy ^a | 1 year | 0/35 (0%) | 3/35 (9%) | 0.17 (0.01, 0.44) |
| Protocol S | Vitrectomy ^a | 2 year | 3/147 (2%) | 22/155 (14%) | 0.14 (0.04, 0.47) |

Source: Text, Gross et al 2015; Supplementary Table 3 to 5, Lang et al 2020.

AE = adverse events, CI = confidence interval, PRP = panretinal photocoagulation laser, RR = relative risk, SAE = serious adverse event; TEAE = treatment-emergent adverse event

Bold indicates statistically significant results.

Benefits/harms

- 6.31 No clinically meaningful gains in BCVA (ie ≥ 10 letters) were experienced in the PRIDE trial; and Protocol S trial data for BCVA was confounded as the trial enrolled patients with PDR and DMO at baseline.
- 6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with ranibizumab in comparison with PRP:
- Patients would experience approximately a 2.8 mm² greater reduction in NV over 1 year (PRIDE, Table 12).
 - Approximately 16 fewer patients will develop clinically significant DMO over 5 years (Protocol S trial, Table 11).

Clinical claim

- 6.33 The submission described ranibizumab as superior in terms of effectiveness and non-inferior in terms of safety compared to PRP. The proposed superiority claim was based on visual acuity gain and reduction in risk of clinically significant DMO.
- 6.34 The ESC considered the superiority claim for comparative clinical effectiveness was partially supported.
- 6.35 The ESC noted that there was a statistically significant decrease in NV and a decreased risk of developing DMO supporting the claim for superior comparative clinical effectiveness.
- 6.36 The ESC considered the superiority claim for comparative clinical effectiveness in improving visual acuity was not supported. While ranibizumab showed early improvements in BCVA relative to PRP, these benefits were not consistently clinically

Public Summary Document – May 2025 PBAC Meeting

meaningful or sustained long-term. Limited improvement in vision is not unexpected due to PDR treatment side effects often impacting vision, particularly in patients treated with PRP. The Pre-PBAC response acknowledged the high rate of cross over created a limitation to determine a true comparison between ranibizumab and PRP. However, an assertion of an overestimated treatment benefit for this reason should be balanced by an equal assessment of the impact of crossover in the PRP group where the response considered that on balance, ranibizumab is highly likely to be clinically superior to PRP in terms of visual acuity.

- 6.37 The ESC further noted, PDR treatment aims to reduce progression to DMO and decrease NV, in which ranibizumab achieves favourability when compared to PRP.
- 6.38 The ESC considered the safety claim of non-inferiority compared to PRP was supported. The ESC noted the reduction in vitrectomies which may lead to a significant decrease in the surgical procedures needed to treat this serious and complex complication.
- 6.39 The PBAC considered the claim of superior comparative effectiveness was supported for change in NV and risk of DMO and was uncertain but reasonable for improvement in visual acuity.
- 6.40 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.41 The submission presented a cost utility analysis, using a 26-health state Markov model of ranibizumab compared to PRP for the treatment of PDR. ESC considered the CUA was a reasonable approach, given the reduced risk of DMO.
- 6.42 A summary of the model structure and key inputs along with the rationale of economic evaluation are summarised in Table 15.

Public Summary Document – May 2025 PBAC Meeting

Table 15: Summary of model structure, key inputs and rationale

| Component | Summary |
|---------------------------------|--|
| Type of analysis | Cost-utility analysis |
| Treatment | Ranibizumab vs laser photocoagulation |
| Time horizon | 20 years in the model base case vs 5 years in the Protocol S trial (2-year data used for most model inputs) and 1 year in the PRIDE trial. A time horizon of 15 years was used in the DMO submission for ranibizumab. |
| Outcomes | QALYs gained, DMO cases avoided |
| Method used to generate results | Markov model |
| Health states | 26 alive health states, including 13 non-DMO and 13 DMO health states. Health states within DMO and non-DMO states are identical based on 5-letter increments of BCVA from ≥ 90 to < 35 . 1 dead health state |
| Cycle length | Annual; in clinical practice, a ranibizumab injection is recommended once a month up to 3 months. Continued treatment may be needed as per treatment response. |
| Transition probabilities | Demographic information (age, gender) was sourced from the PRIDE trial. Transition probabilities for ± 10 or ± 15 -letter change, probability of DMO and probability of bilateral were sourced from the Protocol S trial; ± 5 -letter change probabilities were informed by the PRIDE trial. Mortality was based on ABS life tables. |
| Extrapolation method | The analysis employed 2-year data from the Protocol S trial (proportion of patients with a 10- or 15-letter change in BCVA) and 1-year data from the PRIDE trial (proportion of patients with a 5-letter change in BCVA). Beyond the 2-year follow-up period, the model assumed a constant probability of BCVA progression of 20% per year across both arms (i.e. 20% of patients within each health state progress to the next worse BCVA health state). The annual probability of developing DMO was informed by 5-year follow-up data from Protocol S. These inputs appear to be held constant over the duration of the model (i.e. there is an ongoing treatment benefit beyond trial follow-up and, more importantly, even once treatment ceases). Treatment duration is assumed to be 6 years in the base case. Once patients have developed DMO, a constant probability of BCVA progression of 20% per year across both arms was assumed. The submission suggests this assumption (applied for both progression through DMO health states and progression through non-DMO health states beyond 2 years) was informed by Protocol S and is consistent with the previous DMO submission to PBAC. |
| Health-related quality of life | Sourced from the RESTORE trial of ranibizumab for DMO. Base case utilities for the 13 BCVA health states, defined by BCVA scores from ≥ 90 to < 35 , were as follows: 0.86, 0.86, 0.86, 0.86, 0.81, 0.81, 0.80, 0.80, 0.77, 0.77, 0.76, 0.76, 0.61. |
| Discount rate | 5% costs and outcomes; sensitivity analyses on 3.5% and 0% |
| Software package | Microsoft Excel |

Source: Constructed during the evaluation based on the information provided in the submission, Table 3.2, pp125-126 of the submission. ABS = Australian bureau of statistics, BCVA = best-corrected visual acuity, DMO = diabetic macular oedema, ICER = incremental cost-effectiveness ratio, QALY = quality adjusted life year.

6.43 Demographic characteristics of the model cohort (start age 53.5 years; 68.9% male) were defined by the PRIDE trial. The baseline distribution across BCVA health states and the proportion of patients with bilateral disease were informed by the Protocol S trial. Transition probabilities defining patient movement between the 26 BCVA health states were mainly informed by the Protocol S trial data at 2 years. The probability of 5 letter loss or gain in BCVA at 1 year were supplemented with data from the PRIDE trial.

Public Summary Document – May 2025 PBAC Meeting

- 6.44 Although 5 years follow up data were available in the Protocol S trial, the submission considered these results to be unsuitable to inform transition probabilities in the model given there was a high number of patients with DMO at baseline and the results were confounded by a high proportion of treatment switching to ranibizumab in the laser arm over 5 years.
- 6.45 The 2-year follow-up data was taken from the whole trial population as opposed to the subgroup of patients without DMO at baseline, which would be more applicable to the model population. The ESC considered it was appropriate to present a sensitivity analysis based on the 2-year data for the subgroup of patients without DMO at baseline (see Table 19). As noted above (see paragraph 6.17), BCVA improvements were more pronounced in patients with baseline DMO, therefore use of the whole trial population would bias the results in favour of ranibizumab.
- 6.46 The time horizon was a key driver of the economic model, suggesting a large proportion of the treatment benefit (costs and QALYs) accumulated over the extrapolation period.
- 6.47 The annual probability of transition from non-DMO to DMO was shown to have a high impact on the ICER in sensitivity analyses performed in the submission. The annual probabilities, derived from 5-year follow-up data from Protocol S (4.8% in ranibizumab vs 9.1% in PRP), appear to be held constant over the duration of the model, without any clear rationale for this. In effect, there is an ongoing treatment benefit beyond trial follow-up, and, more importantly, even once treatment ceases (assumed to be 6 years in the base case). The ESC noted that the smaller proportion of patients in the ranibizumab arm developing DMO may be exaggerated, with the incidence surpassing non-DMO cases after 14 years. In contrast, the PRP arm experiences a more rapid onset of DMO, with the number of cases exceeding non-DMO cases within 7 years. The PSCR stated it is appropriate to assume there would be some residual treatment effect with ranibizumab. This is consistent with the goal of ranibizumab treatment for PDR and DMO, which is long-term sustained benefit. The ESC accepted that while there may be some lingering treatment effect, it was unlikely this would be sustained for the full model time horizon. Overall the ESC did not consider the constant annual probabilities over the duration of the model was adequately justified or clinically plausible, and incorporation of a treatment waning effect would be more appropriate.
- 6.48 Treatment duration had a significant impact on the ICER. Sensitivity analyses performed in the submission showed that when treatment is reduced to 3 years, the ICER was 1% lower than the base case and ranibizumab became dominant. Conversely, extending treatment duration to 8 years resulted in an ICER that was 1% higher than the base case. Changing the assumed treatment duration in the model affected estimated costs only; incremental effectiveness calculations are not impacted. The PSCR noted clinician feedback indicated ongoing treatment with ranibizumab is unlikely and it was asserted the 6-year treatment duration applied in the model base case was conservative compared to previous ranibizumab models for DMO

Public Summary Document – May 2025 PBAC Meeting

(Ranibizumab PSD, July 2014 PBAC Meeting), which assumed a treatment duration of only 3 years. The ESC considered it may be appropriate to align the treatment duration to 3 years, noting adjustment to the treatment benefit would also need to also be factored in.

- 6.49 The source of clinical data for the transition probabilities appears to be a key model driver. Use of PRIDE trial data alone instead of Protocol S trial data increases the ICER by █%. While there are differences in study populations and treatment groups across the 2 trials, it was unexpected that the 2 included studies would produce such different economic outcomes. Some key structural differences between the 2 scenarios were identified during the evaluation, which may be contributing to this large difference: trial-based probabilities were applied for 2 years in the base case compared to 1 year in the PRIDE scenario; a probability of a 15-letter improvement or worsening was included in the base case but not in the PRIDE scenario. PRIDE data remained a valid test scenario, as it reflects a plausible treatment regimen. Patients are expected to receive monthly treatments over the course of 1 year, aligned with the standard of care for DMO albeit for a shorter duration (i.e. monthly treatment for up to 3 months).
- 6.50 The submission included a scenario analysis adopting a societal perspective to capture the impact on non-health benefits within the ICER. This scenario modelled the effect of lost productivity due to vision impairment for patients aged <67 years and a BCVA score ≤44. Ranibizumab was dominant in this scenario. This approach favours ranibizumab, which may overestimate its cost effectiveness, as several assumptions need to be considered. While short-term absence of work and productivity losses are assumed to be recovered, critical factors including employer capacity, the impact of replacement workers, and accuracy of the utility capture require further consideration to fully evaluate the effect of the ranibizumab treatment.
- 6.51 The key drivers of the model are presented in Table 16.

Table 16: Key drivers of the model

| Description | Method/Value | Impact Base case: \$█/QALY gained |
|--------------|---|--|
| Discounting | Discount rate of 5% for both costs and effects in the base case. Rates of 0% and 3.5% were used in sensitivity analyses, with these analyses resulting in high variation in the ICER. | High, favours ranibizumab. Use of a 0% discount rate inverted the incremental costs to negative, resulting in ranibizumab being dominant. Use of a 3.5% discount rate resulted in an ICER of \$█ ² per QALY gained, which is █% lower than the base case. |
| Time horizon | The base case model adopted a time horizon of 20 years. A range of alternate time horizons (5 years to lifetime) were tested in sensitivity analyses. The results showed significant fluctuations in ICER values. | High, favours ranibizumab. Use of 5-, 10- and 15-year time horizons increased the ICER by █%, █% and █%, respectively. For time horizons >25 years, ranibizumab was dominant. |

Public Summary Document – May 2025 PBAC Meeting

| Description | Method/Value | Impact Base case: \$█████ ¹ /QALY gained |
|---|---|---|
| Bilateral proportion | Data from the Protocol S trial were used to inform the proportion of patients treated in both eyes (i.e. bilateral proportion). The base case value was varied ±10% in sensitivity analysis. Literature-informed proportions were also explored during the evaluation. For instance, a study by Dhoot et al 2023, indicated around 50% patients developed DMO in second eye over 2 years; a study by Alsoum et al 2023 showed that 64% of patients developed DMO in second eye within 1 year. The outcomes were highly uncertain. | High, favours ranibizumab. Use of +10% of base case bilateral proportion increased the ICER to \$█████ ³ per QALY gained (█████%). Use of -10% reduced the ICER by █████%. The literature-based sensitivity analyses performed during evaluation reported significant increases in the ICER (█████% to █████%). |
| Treatment duration | Treatment duration was assumed to be 6 years for the base case. Three and 8 years were applied in sensitivity analyses undertaken in the submission. The ICER was highly sensitive to changes in the assumed treatment duration. Changing the assumed treatment duration in the model affected estimated costs only. | High impact (direction uncertain). Reducing the treatment duration to 3 years inverted the incremental costs to negative; however, incremental QALYs remain same, with ranibizumab becoming dominated over laser photocoagulation. Increasing the treatment duration to 8 years increased the ICER by █████% (i.e. \$█████ ⁴ per QALY gained). |
| DMO probability | The submission modelled a 4.8% annual transition probability of DMO for the ranibizumab arm and a 9.1% annual probability of DMO in the laser photocoagulation arm. The submission undertook sensitivity analysis varying the annual probability of DMO (i.e., ±1% to the base case value probability) in the ranibizumab arm between 3.9% and 5.8%. | High, favours ranibizumab. Use of 5.8% annual DMO transition probability increased ICER by █████%. Reducing the annual DMO transition probability to 3.9% resulted in ranibizumab becoming dominated over laser. |
| Alternate source for transition probabilities | The submission used demographic characteristics from the PRIDE trial and transition probabilities from the Protocol S trial. The model allows users to select an alternate source for the transition probabilities, whereby transitions are sourced from PRIDE trial data alone instead of Protocol S trial data (supplemented by PRIDE data). This remains valid to test scenario, in which patients are expected to receive 12 monthly treatments over the course of 1 year, align with the standard of care for DMO. | High, favours ranibizumab. The use of PRIDE trial data increased the ICER by █████% (i.e. \$█████ ⁵ per QALY gained). |
| Perspective | A scenario adopting a societal perspective, which captures productivity losses due to vision loss, was also presented in the submission. | High, favours ranibizumab. The inclusion of productivity losses resulted in ranibizumab becoming dominant (less costly, more effective). |

Source: Constructed during the evaluation based on the information provided in the submission.

DMO = diabetic macular oedema, ICER = incremental cost-effectiveness ratio, QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

- ¹ \$25,000 to < \$35,000
- ² \$5,000 to < \$15,000
- ³ \$35,000 to < \$45,000
- ⁴ \$45,000 to < \$55,000
- ⁵ \$155,000 to < \$255,000

6.52 The results of modelled economic evaluation are presented in Table 17.

Public Summary Document – May 2025 PBAC Meeting

Table 17: Results of the stepped economic evaluation

| Step and component | Ranibizumab | Laser | Increment |
|--|-------------|-----------|--|
| Step 1: Costs per DMO case prevented at 5 years | | | |
| Cost | \$█ | \$35,074 | \$█ |
| DMO cases prevented | 0.21 | 0.37 | 0.16 |
| Incremental cost per DMO case prevented | | | \$ ¹ per DMO prevented |
| Step 2: Cost per QALY at 5 years | | | |
| Cost | \$█ | \$35,074 | \$█ |
| QALYs | 4.42 | 4.38 | 0.04 |
| Incremental cost/extra QALY gained | | | \$ ² per QALY |
| Step 3: Cost per QALY at 20 years | | | |
| Cost | \$█ | \$110,269 | \$█ |
| QALYs | 10.59 | 10.44 | 0.15 |
| Incremental cost/extra QALY gained | | | \$ ³ per QALY \$ ⁴ per QALY * |

Source: Table 3.23, p147 of the submission.

DMO = diabetic macular oedema, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year.

*The ranibizumab and DMO treatment costs in the model was based on the AEMP rather than the DPMQ. The base case ICER using the DPMQ has been updated using the DPMQ of \$█ for ranibizumab.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$355,000 to < \$455,000

³ \$15,000 to < \$25,000

⁴ \$25,000 to < \$35,000

6.53 The disaggregated summary of cost impacts in the economic evaluation are summarised in Table 18.

Table 18: Disaggregated summary of cost impacts in the economic evaluation*

| Cost items | Ranibizumab | Laser | Incremental cost | % of total incremental cost |
|-----------------------------|-------------|--------------|------------------|-----------------------------|
| Treatment | \$█ | \$2,807.20 | \$█ | █% |
| Co-medications | \$379.05 | \$0.00 | \$379.05 | █% |
| Administration ^a | \$8,111.20 | \$0.00 | \$8,111.20 | █% |
| Monitoring | \$4,722.41 | \$1,089.85 | \$3,632.56 | █% |
| Falls | \$12,087.28 | \$12,187.13 | -\$99.85 | -█% |
| Community | \$48,319.91 | \$52,853.51 | -\$4,533.61 | -█% |
| DMO treatment | \$26,683.53 | \$41,331.18 | -\$14,647.65 | -█% |
| Total | \$█ | \$110,268.87 | \$█ | 100% |

Source: Table 3.24, p148 of the submission.

DMO = diabetic macular oedema.

^aFor ranibizumab, administration cost was informed by MBS item 42740 and applied per injection. The cost of laser treatment was sourced from the relevant MBS item 42809 for laser photocoagulation treatment, which includes the cost of administration.

*treatment costs were calculated based on AEMPs.

6.54 Treatment costs and administration costs (sourced from MBS item 42740 and applied per injection) were key drivers of incremental costs. These costs were much higher in the ranibizumab arm compared to the PRP arm. In the ranibizumab arm, the cost of falls, community-related costs and DMO treatment were lower compared to laser, indicating cost-savings in these areas.

6.55 Overall QALYs accumulated for the laser photocoagulation arm in the DMO BCVA health states were 53% higher compared to ranibizumab. This was driven by patients

Public Summary Document – May 2025 PBAC Meeting

in the ranibizumab arm spending less time in the DMO health states relative to patients in the laser photocoagulation arm.

6.56 The results of key sensitivity analyses are summarised in Table 19. The results have been updated to reflect the DPMQ rather than AEMP for ranibizumab and subsequent treatment for DMO.

Table 19: Sensitivity analyses

| Analysis | Incremental cost | Incremental QALY | ICER | % change from base case |
|---|------------------|------------------|-------------------|-------------------------|
| Base case (AEMP \$█) | \$█ | 0.15 | \$█ ¹ | - |
| Base case (DPMQ \$█) | \$█ | 0.15 | \$█ ² | - |
| Discount rate (base case 5% costs and outcomes) | | | | |
| 0% costs and outcomes | -\$█ | 0.26 | dominant | -% |
| 3.5% costs and outcomes | \$█ | 0.18 | \$█ ³ | -% |
| Time horizon (base case 20 years) | | | | |
| 5 years | \$█ | 0.04 | \$█ ⁴ | % |
| 10 years | \$█ | 0.09 | \$█ ⁵ | % |
| 15 years | \$█ | 0.13 | \$█ ⁶ | % |
| 25 years | \$█ | 0.18 | \$█ ³ | -% |
| 30 years | -\$█ | 0.19 | dominant | -% |
| 40 years | -\$█ | 0.21 | dominant | -% |
| Lifetime (50 years) | -\$█ | 0.21 | dominant | -% |
| Proportion bilateral 29.2% for base case | | | | |
| Proportion bilateral 19.2% | \$█ | 0.16 | \$█ ³ | -% |
| Proportion bilateral 39.2% | \$█ | 0.16 | \$█ ⁷ | % |
| Proportion bilateral 50% (Dhoot et al 2020) | \$█ | 0.16 | \$█ ⁶ | % |
| Proportion bilateral 64% (Alsalous et al 2023) | \$█ | 0.16 | \$█ ⁸ | % |
| Treatment duration ceasing at 6 years for base case | | | | |
| Treatment duration ceasing at 3 years | -\$█ | 0.16 | dominant | -% |
| Treatment duration ceasing at 8 years | \$█ | 0.16 | \$█ ⁹ | % |
| Probability of DMO at 5-year follow up: based on Protocol S (4.8% annual probability, ranibizumab arm) for base case | | | | |
| Probability of DMO, 3.9% ranibizumab arm (RR - 0.1 applied) | \$█ | 0.16 | \$█ ¹⁰ | -% |
| Probability of DMO, 5.8% ranibizumab arm (RR +0.1 applied) | \$█ | 0.16 | \$█ ⁹ | % |
| Healthcare payer perspective for base case | | | | |
| Societal perspective | -\$█ | 0.15 | dominant | -% |
| Transition probabilities (Protocol) and demographics (PRIDE) for base case | | | | |
| Both transition probabilities and demographic from Protocol S | \$█ | 0.16 | \$█ ² | -% |
| Both transition probabilities and demographic from PRIDE | \$█ | 0.04 | \$█ ¹¹ | % |
| BCVA transition probabilities | | | | |
| 2-year BCVA outcomes for 'without DMO at baseline' subgroup' | \$█ | 0.12 | \$█ ⁷ | +% |

Source: Constructed during the evaluation, Lucentis PDR model in Excel, Table 3.27, pp149-150 of the submission.

DMO = diabetic macular oedema, ICER = incremental cost-effectiveness ratio, QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$25,000 to < \$35,000

³ \$5,000 to < \$15,000

*Public Summary Document – May 2025 PBAC Meeting*⁴ \$355,000 to < \$455,000⁵ \$135,000 to < \$155,000⁶ \$55,000 to < \$75,000⁷ \$35,000 to < \$45,000⁸ \$75,000 to < \$95,000⁹ \$45,000 to < \$55,000¹⁰ \$0 to < \$5,000¹¹ \$155,000 to < \$255,000

6.57 The ESC noted the ICERs should be presented using the DPMQs for PBS medicines rather than AEMPs. The ICERs in Table 19 have been updated to reflect this. The ESC considered additional sensitivity analyses would be informative:

- BCVA outcomes sourced from the ‘without DMO at baseline’ subgroup of the Protocol S trial (see final row in Table 19)
- Include treatment waning for DMO reduction following treatment discontinuation (the sponsor is requested to provide this)
- Remove the treatment effect of improvement in BCVA, given the clinical significance of the trial results for this outcome is uncertain (the sponsor is requested to provide this)

6.58 The pre-PBAC response acknowledged the economic issues raised by ESC and presented a range of analyses and model revisions as requested. To reduce any residual uncertainty for the PBAC, the sponsor revised the price to the effective DMO price (DPMQ \$¹¹).

6.59 The pre-PBAC response noted a treatment waning for progression to DMO was incorporated into a revised economic model. The modified scenario treatment waning after year 6 (with base case treatment duration of 6 years), and treatment waning applied after year 5 (with a reduced treatment duration of 5 years, aligning with the duration of follow-up in Protocol S), produced ICERs of \$5,000 to < \$15,000 and \$0 to < \$5,000 per QALY, respectively. In the scenario in which the BCVA benefit is removed, no incremental QALYs are captured because utilities are captured only as a function of BCVA. However, the results presented in the Pre-PBAC response erroneously suggest the incremental costs under the ‘no BCVA benefit’ scenario are equivalent to those under the corresponding scenario including BCVA benefits. In the model, costs for the treatment of falls, as well as community care costs, are assigned as a function of BCVA. Therefore, under a scenario in which the BCVA benefit is removed, the cost offsets attributed to ranibizumab through reduced community care and fall-related expenses should also be removed.

An updated sensitivity analyses incorporating the pre-PBAC responses was included in Committee-In-Confidence information

6.60 Table 21.

Public Summary Document – May 2025 PBAC Meeting

Table 20: Sensitivity analyses from pre-PBAC responses on revised base case

| Parameter | Incremental Cost | Incremental QALYs | ICER |
|--|------------------|-------------------|---------------------------------------|
| Submission base case (AEMP and published prices) | \$█ | 0.15 | \$█ ¹ |
| Revised effective DPMQ of \$█ in PDR | -\$█ | 0.15 | Ranibizumab DOMINANT |
| Revised effective DPMQ + treatment waning after year 6 | \$█ | 0.15 | \$█ ² |
| Revised effective DPMQ + treatment duration of 5 years + treatment waning after year 5 | \$█ | 0.15 | \$█ ³ |
| Revised effective DPMQ + treatment waning after 6 years + remove BCVA benefit | \$█ ² | 0 | incremental cost per DMO case avoided |

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$5,000 to < \$15,000

³ \$0 to < \$5,000

⁴ \$5,000 to < \$15,000

6.61 An updated sensitivity analyses incorporating the pre-PBAC responses and commercial-in-confidence effective prices for downstream DMO treatments was included in Table 21.

Committee-In-Confidence information

Table 21: Sensitivity analyses from pre-PBAC responses on revised base case

End Committee-In-Confidence information

Drug cost/patient/year

6.62 The ranibizumab costs in year 1 was \$█ per patient followed by \$█ in year 2, \$█ in year 3, and \$█ in years 4–5. The number of injections per patient decreases from an average of 9.17 in year 1 to 4.26 in year 2, 3.88 in year 3 and 3.75 in years 4 and 5. These costs and drug regimen align with the Protocol S trial and in the model. Treatment duration is expected to be up to 6 years. The total cost of ranibizumab over the course of treatment, assuming costs from year 5 onwards are the same, was \$█ per

Public Summary Document – May 2025 PBAC Meeting

patient. This cost is calculated using the per-patient cost in the financial model, which was based on DPMQ, whereas the economic model used AEMP. These estimated costs were based on the original submission price and not the revised lower price in the pre-PBAC response.

6.63 A comparison of drug cost per patient across the trial, economic and financial model are summarised in Table 22.

Table 22: Drug cost per patient for proposed and comparator drugs

| | Proposed drug Trial dose and duration | | Proposed drug Model | Proposed drug Financial estimates |
|--|--|--------------------------|--|---|
| Mean dose | 0.5 mg/injection | | 0.5mg/injection | 0.5mg/injection |
| Mean duration | 5 years follow-up | | 6 years | 6 years |
| Average number of injections per patient per year | Per eye | Per patient ^a | Year 1: 9.17 ^a Year 2: 4.26 ^a Year 3: 3.88 ^a Year 4: 3.75 ^a Year 5+: 3.75 ^a | Year 1: 9.17 ^a Year 2: 4.26 ^a Year 3: 3.88 ^a Year 4 6: 3.75 ^a Year 5+ 3.75 ^a |
| | Year 1: 7.10 | Year 1: 9.17 | | |
| | Year 2: 3.30 | Year 2: 4.26 | | |
| | Year 3: 3.00 | Year 3: 3.88 | | |
| | Year 4: 2.90 | Year 4: 3.75 | | |
| | Year 5: 2.90 | Year 5: 3.75 | | |
| Cost/patient/year | Year 1: \$ | Year 1: \$ | Year 1: \$ | Year 1: \$ |
| | Year 2: \$ | Year 2: \$ | Year 2: \$ | Year 2: \$ |
| | Year 3: \$ | Year 3: \$ | Year 3: \$ | Year 3: \$ |
| | Year 4 to 5: \$ | Year 4 to 5: \$ | Year 4 to 5: \$ | Year 4 to 5: \$ |

Source: Table 3.12, Table 3.14 of the submission, Table 2 pp 8-9 of the Protocol S trial study, Lucentis PDR model sheet, Tx costs of the submission. Italicised values have been calculated.

Note: Comparator was removed from table because cost covered by MBS in laser arm.

^a Proportion of bilateral (29.18% informed by Protocol S trial) plus trial informed injection per eye (Protocol S trial) was applied for model.

^b Trial based average injection per eye (Protocol S trial) was multiplied by cost of ranibizumab injection per vial (sponsor estimated (\$ effective AEMP))

^c Average number of injections per patient per year was multiplied by the unit cost of ranibizumab injection (\$ effective price: DPMQ)

Estimated PBS usage & financial implications

6.64 The submission was considered by DUSC.

6.65 The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of ranibizumab for the treatment of PDR without DMO.

6.66 Key inputs and relevant data sources used in the financial impact analyses are summarised in Table 23 to Table 25. Table 24

Public Summary Document – May 2025 PBAC Meeting

Table 23: Data sources and parameter values applied in the utilisation and financial estimates – eligible population

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|---|--|---|--|--|
| Total Australian population; aged 18 to 100 years | Yr 1: 21,744,502 Yr 2: 22,073,220 Yr 3: 22,393,101 Yr 4: 22,714,178 Yr 5: 23,030,499 Yr 6: 23,344,513 | ABS data | The source and estimation seemed reasonable. | DUSC considered this reasonable |
| Incident diabetic patients | Yr 1: 38,270 Yr 2: 38,849 Yr 3: 39,412 Yr 4: 39,977 Yr 5: 40,534 Yr 6: 41,086 | The incidence of diabetes (0.176%) was sourced from the most recent AIHW data (AIHW 2024 ^a) | Australian population × incident rate of 0.176% The incidence and prevalence likely to be underestimated. AIHW and Diabetes Australia indicated that incidence and prevalence rates of diabetes are likely underestimated, Diabetes Australia 2023 report has suggested that the prevalence rate could be as high as 7.5% | The submission uses incidence for all ages, age-standardised to the 2001 Australian population. DUSC considered this is an underestimate (population has aged since 2001, and incidence is higher in people aged 18+ years). DUSC considered that the AIHW ² incidence for 2021 for population aged 18+ years be used, i.e. 0.240% was more appropriate. Yr 1: 52,187 Yr 2: 52,976 Yr 3: 53,743 Yr 4: 54,514 Yr 5: 55,273 Yr 6: 56,027 |
| Prevalent diabetic patients | Yr 1: 1,217,692 Yr 2: 1,256,541 Yr 3: 1,295,953 Yr 4: 1,335,930 Yr 5: 1,376,463 Yr 6: 1,417,550 | The prevalence of diabetes (5.6%) was sourced from the Diabetes Australia 2023 report. | Yr 1, Australian population × prevalent rate of 5.6% Yr 2+, incident diabetic patients in current year + prevalent diabetic patients in last year. This approach was not reasonable, as it resulted in the current year's incidence estimate being counted twice in the total diabetic population estimate. | DUSC considered that the revised approach used in the PSCR such that incident patients in the current year are not included in the prevalent patient count for that year was reasonable. The approach of sequentially adding incident patients to the number of prevalent patients in year 1 assumes that no patients leave the prevalent pool (die or migrate). Therefore, the number of prevalent patients is overestimated. DUSC considered that consideration be given to estimating annual mortality in the diabetic population and subtracting this number from the prevalent pool. According to the AIHW ³ , diabetes contributed to 21,900 deaths in 2022. Diabetes Australia prevalence is approximate and is for all ages. AIHW 2021 prevalence for 18+ years is 6.47%. |

² <https://www.aihw.gov.au/reports/diabetes/diabetes/data>

<https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/dec-2021#data-downloads>

³ <https://www.aihw.gov.au/reports/diabetes/diabetes/contents/impact-of-diabetes/diabetes-deaths>

Public Summary Document – May 2025 PBAC Meeting

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|------------------------|--|---|--|---|
| | | | | Using 6.47% prevalence and ABS population estimate yields: Yr 1: 1,406,869 DUSC considered that this figure be used for Year 1. This is comparable with the December 2024 NDSS all ages snapshot figure of 1,456,279 ⁴ |
| Prevalent PDR patients | Yr 1: 51,143 Yr 2: 59,336 Yr 3: 67,741 Yr 4: 76,361 Yr 5: 85,198 Yr 6: 94,254 | The prevalent rate of 4.2% was the median value of 2.1% and 6.3%, sourced separately from the AusDiab 2002 population-based study (Tapp et al 2003) ⁴ and a more recent Australian clinic-based study (Liew et al 2023). | Yr 1, prevalent diabetic patients × prevalent rate of 4.2% Yr 2+, incident PDR patients in last year + prevalent PDR patients in last year | DUSC considered that the approach used assumes that no patients leave the prevalent pool. The Liew et al paper was based on a tertiary retinal clinic population so the prevalence of PDR is likely to be an overestimate. A population-based study in Melbourne in 1992-96 (McKay et al, 2000) reported a PDR rate of 4.2% in people aged 40+ with self-reported diabetes. Overall, the median value of 4.2% is likely to be an overestimate, considering the AusDiab prevalence (2.1%) and potential improvements in management of diabetes over time, but there is a lack of recent Australian population-based estimate. DUSC considered that a figure of 4.2% be used ⁵ . |
| Incidence PDR patients | Yr 1: 8,193 Yr 2: 8,405 Yr 3: 8,620 Yr 4: 8,837 Yr 5: 9,056 Yr 6: 9,278 | The incidence rate of 0.68% was sourced from a UK population-based study (Jones et al 2012). | Incident rate × total diabetic patients excluding prevalent PDR patients Likely underestimated because the incidence rate after 10 years follow-up was 1.5% (Jones et al) | DUSC considered that this is an overestimate. The Jones et al. incidence rate of 0.68% is a cumulative incidence over 5 years. The average annual incidence rate can be estimated as $0.68/5=0.136\%$. This is consistent with the 10-year cumulative incidence from the same study of 1.5%, producing an average annual incidence of $1.5/10=0.15\%$. DUSC considered that 0.15% be used. DUSC noted that this reduces the annual number of incident cases substantially. |
| Grandfathered patients | █ ¹ | The number of grandfathered patients was estimated by applying the NPDR/PDR ratio in | Including the grandfathered population in the adjusted prevalence pool would result in | DUSC considered that the estimated number of grandfathered patients is appropriate. |

⁴ <https://www.aihw.gov.au/reports/diabetes/diabetes/data>

<https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/dec-2021#data-downloads>

⁵ McKay, R., C.A. McCarty, and H.R. Taylor, *Diabetic retinopathy in Victoria, Australia: the Visual Impairment Project*. *Br J Ophthalmol*, 2000. 84(8): p. 865-70.

Public Summary Document – May 2025 PBAC Meeting

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|--|--|---|--|---|
| | | 2024 to the total number of patients accessing ranibizumab through the Novartis compassionate access program. | double counting. The evaluation's sensitivity analysis addressed this by excluding the grandfathered population, considering them ineligible and outside the prevalence pool. | |
| Incidence of PDR patients eligible for treatment | Yr 1: 1,639 Yr 2: 1,681 Yr 3: 1,724 Yr 4: 1,767 Yr 5: 1,811 Yr 6: 1,856 | Eligible rate of 20%, assumed based on KOL. According to WESDR report in Section 1.1.2 in the submission, DMO was present in 71% of eyes with PDR, which was outside the PICO scope. Given other additional restrictions such as contraindications and patient selection criteria, the estimated eligible rate of 20% was considered reasonable, based on expert opinion. | Incident PDR × eligible rate | Based on proposed restriction which excludes DMO, DUSC considered that 30% may be a more appropriate estimate. DUSC considered that >30% of PDR patients will be eligible if the restriction is changed to that recommended above (PDR patients with DMO but no vision impairment + PDR patients without DMO) |
| Prevalent PDR patients eligible for treatment | Yr 1: 9,525 Yr 2: 8,324 Yr 3: 6,659 Yr 4: 5,327 Yr 5: 4,262 Yr 6: 3,409 | | Yr 1, prevalent PDR patients × eligible rate – grandfather patients Yr 2+, prevalent PDR patients in Yr 1 – sum of eligible prevalent population in earlier years × eligible rate | Based on current restriction which excludes DMO, DUSC considered that 30% may be a more appropriate estimate. DUSC considered that >30% of PDR patients will be eligible if the restriction is changed to that recommended above (PDR patients with DMO but no vision impairment + PDR patients without DMO) |

Source: Table 4.1.1, pp110-112 of the commentary

ABS = Australian Bureau of Statistics, AIHW = Australian Institute of Health and Welfare, CSR = clinical study report, DPMQ = dispensed price for maximum quantity, DMO = diabetic macular oedema, DUSC = Drug Utilisation Sub-Committee, KOL = key opinion leader, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, PDR = proliferative diabetic retinopathy, PICO = population, intervention, comparator, outcome, RPBS = Repatriation Pharmaceutical Benefits Scheme, Yr = year.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

Public Summary Document – May 2025 PBAC Meeting

Table 24: Data sources and parameter values applied in the utilisation and financial estimates – treatment utilisation

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|---|--|---|--|--|
| Uptake rate of incident patients | █% | Assumption. The evaluation noted the appropriateness of the assumption unclear with no source provided | Uptake rate assumed to remain constant over time | DUSC considered that a significant number of ophthalmologists may elect to change their practice if a PBS subsidised intravitreal anti-vascular endothelial growth factor (VEGF) treatment becomes available, and this will skew towards ranibizumab over PRP - so █% may be an underestimate. |
| Uptake rate of prevalent patients | █% | | | DUSC considered that for prevalent patients, assuming previous treatment with PRP, 5% is a more likely uptake rate for ranibizumab. |
| Incident patients initiating treatment | Yr 1: █ ¹ Yr 2: █ ¹ Yr 3: █ ¹ Yr 4: █ ¹ Yr 5: █ ¹ Yr 6: █ ¹ | Calculated | Incidence of PDR patients eligible for treatment × uptake rate of incident patients (█%) | DUSC considered that this estimate was highly dependent on the uptake rate. |
| Prevalent patients initiating treatment | Yr 1: █ ¹ Yr 2: █ ¹ Yr 3: █ ¹ Yr 4: █ ¹ Yr 5: █ ² Yr 6: █ ² | Calculated | Prevalent PDR patients eligible for treatment × uptake rate of prevalent patients (█%) If the low uptake was due to a significant proportion of the prevalent population accessing treatment through the compassionate access program, then excluding the grandfathered population again might lead to over-adjustment. | DUSC considered that this estimate was highly dependent on the uptake rate. |
| Continuing treatment rate | Yr 1: 100% Yr 2: 84% Yr 3: 73% Yr 4: 65% Yr 5: 61% Yr 6: 61% | Protocol S discontinuation rate Gross et al (2018) Protocol S Supplementary materials | Yr 6 is an extrapolation of the 5th year of treatment; no evidence provided. | DUSC considered that this was reasonable. |
| Proportion of eyes not progressing to DMO | Yr 1: 100% Yr 2: 94% Yr 3: 90% Yr 4: 86% Yr 5: 82% Yr 6: 82% | Protocol S proportion of eyes which did not develop DMO Gross et al (2018) Protocol S Supplementary materials | Yr 6 is an extrapolation of the 5th year of treatment; no evidence provided. | DUSC considered that this was reasonable. |

Public Summary Document – May 2025 PBAC Meeting

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|--|--|---|---|---|
| Ranibizumab co-payment split | PBS: 98.05% RPBS: 1.95% | Script volumes for currently listed medicines (i.e. ranibizumab) in calendar year 2024. Relevant PBS items include 10373Y, 10374B, 13134G, and 13165X. | | DUSC considered that this was reasonable. |
| Number of injections per eye per year of treatment | Yr 1: 7.1 Yr 2: 3.3 Yr 3: 3.0 Yr 4: 2.9 Yr 5: 2.9 Yr 6: 2.9 | Gross et al (2018) Protocol S Supplementary These values were derived from the median number of injections for the overall population in the Protocol S trial. Including data for patients with DMO would introduce uncertainty. | Yr 6 is an extrapolation of the 5th year of treatment; no evidence provided. This was consistent with the secondary analysis of the Protocol S trial, which simulated results over 10 years (Hutton et al 2019). | DUSC considered that the Protocol S trial estimates would be more appropriate if the restriction was changed to include DMO. DUSC noted that the PSCR provided a revised financial estimate that use Protocol S figures for numbers of injections in patients without DMO. |
| Scripts dispensed PBS/RPBS total | Yr 1: ³ Yr 2: ⁴ Yr 3: ⁴ Yr 4: ⁴ Yr 5: ⁴ Yr 6: ⁴ | Calculated | Number of PBS/RPBS treated eyes × number of injections per eye per year | DUSC considered that this was reasonable. |

Source: Table 4.1.1, pp110-112 of the commentary

ABS = Australian Bureau of Statistics, AIHW = Australian Institute of Health and Welfare, CSR = clinical study report, DPMQ = dispensed price for maximum quantity, DMO = diabetic macular oedema, DUSC = Drug Utilisation Sub-Committee, KOL = key opinion leader, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, PDR = proliferative diabetic retinopathy, PICO = population, intervention, comparator, outcome, RPBS = Repatriation Pharmaceutical Benefits Scheme, Yr = year.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

Public Summary Document – May 2025 PBAC Meeting

Table 25: Data sources and parameter values applied in the utilisation and financial estimates - costs

| Data | Value | Source | Commentary on the Submission | DUSC Comments |
|-----------------------|----------|---|---|--|
| Proposed medicine | \$786.36 | Published price; DPMQ | ranibizumab 1.65 mg/0.165 mL injection/ 2.3 mg/0.23 mL injection, 0.23 mL vial | DUSC noted the requested price of the proposed medicine |
| | \$█ | Effective price; DPMQ | | |
| PBS co-payment | \$16.66 | Based on PBS/RPBS general patient charge, adjusted by current usage. Relevant items include 10373Y, 10374B, 13134G, and 13165X. | | DUSC considered that this was reasonable. |
| RPBS co-payment | \$7.47 | | | |
| MBS costs | \$342.65 | MBS item 42740 | 29.18% of patients estimated to have bilateral PDR, this equated to 77.4% of scripts incurring the MBS fee. | DUSC noted that this is the Schedule fee. The MBS rebate is 85% of this amount. |
| MBS costs; Comparator | \$513.85 | MBS item 42809 | Population split assumed to be 100% | DUSC noted that this is the Schedule fee. The MBS rebate is 85% of this amount. DUSC considered that this saving may not be realised because ranibizumab may be used as an adjunct to, rather than replace photocoagulation. |

Source: Table 4.1.1, pp110-112 of the commentary

ABS = Australian Bureau of Statistics, AIHW = Australian Institute of Health and Welfare, CSR = clinical study report, DPMQ = dispensed price for maximum quantity, DMO = diabetic macular oedema, DUSC = Drug Utilisation Sub-Committee, KOL = key opinion leader, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, PDR = proliferative diabetic retinopathy, PICO = population, intervention, comparator, outcome, RPBS = Repatriation Pharmaceutical Benefits Scheme, Yr = year.

6.67 Table 26 summarises the estimated number of patient eyes treated and scripts dispensed, the net cost to the PBS/RPBS, and the net cost to the MBS of listing ranibizumab for the treatment of PDR.

Public Summary Document – May 2025 PBAC Meeting

Table 26: Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|--------|--------|--------|--------|--------|--------|
| Estimated extent of use | | | | | | |
| Number of eyes treated | 1 | 1 | 1 | 2 | 2 | 2 |
| Number of scripts dispensed ^a | 3 | 4 | 4 | 4 | 4 | 4 |
| Estimated financial implications of ranibizumab | | | | | | |
| Cost to PBS | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 |
| Patient co-payments to PBS (less) | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 |
| Cost to RPBS | \$ 7 | \$ 7 | \$ 7 | \$ 7 | \$ 7 | \$ 7 |
| Patient co-payments to RPBS (less) | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 | -\$ 6 |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 |
| Net cost to MBS | \$ 7 | \$ 7 | \$ 7 | \$ 7 | \$ 7 | \$ 7 |
| Net cost to Government | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 |

Source: Table 4.15, Table 4.16, Table 4.22, p162-165 of the submission.

MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming number of injections per year as estimated by the submission, from year 1 to 6 (7.1, 3.3, 3.0, 2.9, 2.9, 2.9)

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ \$10 million to < \$20 million

⁶ net cost saving

⁷ \$0 to < \$10 million

- 6.68 Total cost to the PBS/RPBS of listing ranibizumab for PDR was estimated to be \$10 million to < \$20 million in year 6, and a total of \$80 million to < \$90 million in the first 6 years of listing. This estimate was based on the effective price of ranibizumab. Additionally, total cost to the MBS was estimated to be \$0 to < \$10 million in year 6, based on usage of MBS services for intravitreal injection.
- 6.69 The comparator is currently funded via the MBS. Relevant cost saving to the MBS was \$0 to < \$10 million in year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing.
- 6.70 DUSC considered that given the uncertainties and likely underestimates in the data sources and parameter values applied in the utilisation and financial estimates, the net financial impact is likely to be an underestimate. The main issues were:
- The evaluation noted that in the submission, eligible prevalent patients in earlier years were excluded from the adjusted prevalent pool for subsequent years, regardless of whether they were treated. In a scenario analysis undertaken during the evaluation, untreated patients from the eligible prevalent population in earlier years were reintroduced into the prevalent pool. This approach may be more appropriate and help reduce overadjustment. This resulted in a higher total cost.

Public Summary Document – May 2025 PBAC Meeting

- The evaluation noted that the submission sourced the number of injections per patients from the overall Protocol S trial population, which included both PDR patients with and without DMO. However, more applicable data specific to the subgroup of patients without DMO (n = 20) are available. A sensitivity analysis using these alternate data was undertaken in the evaluation. This change had a small impact on the financial estimates.
- The evaluation noted that a conservative uptake rate of 1% for prevalent patients was applied in the submission, with no clear rationale provided. Patients currently accessing treatment through an existing compassionate access program were considered as the grandfathered population. When calculating the number of patients initiating treatment, the grandfathered population was removed from the eligible population, as they were eligible for treatment from year 4. If the low uptake rate was due to patients accessing treatment through the compassionate access program, excluding the grandfathered population could lead to over-adjustment and may underestimate real-world usage.
- The evaluation that the submission highlighted Aboriginal and Torres Strait Islanders people have a markedly higher prevalence of diabetes, vision loss, and blindness compared to their non-Indigenous counterparts, and [diabetes] is a leading cause of vision impairment and blindness in this population. While this is clear, there are uncertainties about the applicability of the ranibizumab clinical trial results, compliance to achieve the desired health outcome given disperse geographical locations, and patient preference (vs PRP) in the Aboriginal and Torres Strait Islanders people. The PSCR noted that vision impairment due to [diabetes] is not only disproportionately high in Aboriginal and Torres Strait Islander people but can have a prolonged impact due to earlier onset of diabetes. Despite the availability of PRP for decades, vision outcomes in the Aboriginal and Torres Strait Islander people remain poor compared to the non-Indigenous Australian population. Affordable access to ranibizumab at the PDR stage can improve health outcomes in Aboriginal and Torres Strait Islander peoples by reducing the number of vitrectomies, freeing health resources in rural/regional locations to more critical procedures and facilitating a fly-in/fly-out treatment model without the need for a laser photocoagulation machine. Cultural factors are known to impact the degree to which public health outcomes are realised, however choosing not to reimburse ranibizumab in this population foregoes any potential public health benefit. Further the PSCR noted that the sponsor agrees that cultural factors can impact the degree to which public health outcomes are realised and stress also the importance of access to culturally sensitive health care services. In 2020, The National Aboriginal Community Controlled Health Organisation (NACCHO) noted that the Closing the Gap measure's reduction in medication co-payments were associated with a relative increase of 39% in the use of medicines, and a reduction of 61% in out-of-pocket spending for patients.

Public Summary Document – May 2025 PBAC Meeting

The NACCHO noted that, “such a measure was particularly important for populations with marked social disadvantage and known high burden of chronic disease”. If ranibizumab is integrated into culturally sensitive health care access programs, and Aboriginal and Torres Strait Islander PDR patients have affordable access, both health and non-health benefits are likely to be realised. DUSC noted that uptake in these populations may be variable. DUSC noted that access to vitrectomy surgery is less accessible in rural and remote settings, making the use of ranibizumab a preferable option. DUSC noted that there may be issues with burden of treatment, adherence, missed doses and loss to follow-up due to ranibizumab’s dosing schedule and that the lesser burden of treatment with photocoagulation may favour photocoagulation in rural and remote settings.

- 6.71 DUSC does not consider that it is likely that ranibizumab will be used in populations beyond the eligible population.
- 6.72 The Pre-PBAC response provided a revised financial estimate that included the revised proposed price (equivalent to the effective price for DMO) and updated population estimates based on DUSC advice. Key changes to the population estimates include applying a diabetes prevalence of 6.47%, using the prevalent diabetic population only, adjusting for diabetes-related mortality (estimated at 21,900 per annum) and updating the PDR incidence to 0.136%. The prevalent uptake rate is 1% as this represents a realistic, conservative estimate. Scenario analyses presented on request from DUSC have been presented for: (a) an increase in diabetes prevalence to 9.95% and (b) an increase in the MBS rebate to 85%, both resulting in minor changes to the overall financial impact.
- 6.73 The revised financials from the pre-PBAC response (see Table 27) include an additional analysis expanding the population to include patients with PDR who progress to DMO, based on the recommendations from DUSC. This included the number of injections from the total Protocol S population and an optimistic eligibility rate of 50%. Inclusion of this population increases the financial cost.

Public Summary Document – May 2025 PBAC Meeting

Table 27: Scenario analysis from pre-PBAC response

| Scenario analysis: If patients with PDR+ DMO are included (DUSC advice population estimates + no. injections inc. total Protocol S + eligibility rate 50%) | | | | | | |
|--|---|------|------|------|------|------|
| Eligible population | 50% | | | | | |
| Total number of eyes | 1 | 2 | 2 | 3 | 3 | 3 |
| Number of injections | From year 1 to 6: 7.1, 3.3, 3.0, 2.9, 2.9, 2.9, as estimated by the total Protocol S cohort | | | | | |
| Net cost PBS / RPBS | \$ 4 | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 |
| Cost to the MBS | \$ 4 | \$ 4 | \$ 4 | \$ 4 | \$ 4 | \$ 4 |
| Cost to Commonwealth | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 | \$ 5 |

Notes: Italic text denotes revised estimates made by the evaluators. Noted the evaluator made a minor correction to the estimated cost to the Commonwealth.

DMO = diabetic macular oedema; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PDR = proliferative diabetic retinopathy.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

Quality Use of Medicines

- 6.74 The submission outlined measures for the safe and effective use of ranibizumab, including pharmacovigilance and risk minimisation activities detailed in the Risk Management Plan (RMP).
- 6.75 Ranibizumab has been used in Australia since 2007 for various retinal conditions, with post market data supporting its efficacy and safety in PDR and across multiple indications.
- 6.76 The submission did not propose additional post market surveillance studies on the quality use of medicines.
- 6.77 The DUSC considered that the burden of treatment with ranibizumab would be high in rural and remote setting where loss to follow-up was possible.

7 PBAC Outcome

- 7.1 The PBAC recommended the PBS listing of ranibizumab for the treatment of proliferative diabetic retinopathy (PDR) with or without diabetic macular oedema (DMO). The PBAC expanded the requested population, originally requested for patients without DMO, based on unmet clinical need and to ensure continuous treatment for patients with PDR that progress to DMO and who have not developed serious vision impairment. The PBAC was satisfied that ranibizumab provides, for some patients, a significant improvement in efficacy over panretinal laser photocoagulation (PRP). The PBAC considered the clinical claim of superior effectiveness versus PRP had been demonstrated despite the limitations in the clinical evidence, with benefits including a reduction in neovascularisation, prevention of DMO and reduced surgeries for vitrectomy. The PBAC recommendation was made on

Public Summary Document – May 2025 PBAC Meeting

- a cost-effectiveness basis to the current treatment option of PRP and at a price equivalent to patients with visual impairment due to DMO.
- 7.2 The PBAC noted the burden of PDR, as highlighted in the consumer comments, and considered there was a clinical need for an alternative to PRP. The PBAC noted the disproportionately high rate of disease among Aboriginal and Torres Strait Islander people who experience significantly higher rates of diabetes-related complications including severe and vision-threatening PDR compared to non-indigenous Australians. Additional treatment options were considered an important factor for this population.
- 7.3 The PBAC recognised PDR as a continuum, and as such considered it would not be appropriate to remove access to ranibizumab once patients develop DMO, but their vision remains intact and thus they would not qualify for PBS reimbursement for DMO. The PBAC agreed with the DUSC suggestion to modify ‘Patient must not have clinically significant macular oedema secondary to diabetic retinopathy’ and replace it with ‘Patient must not be treated with, or does not qualify for, PBS subsidised treatment for macular oedema secondary to diabetic retinopathy’ to enable continuous treatment. The PBAC noted the pre-PBAC response offered a substantial price reduction to enable broader, cost-effective access.
- 7.4 The PBAC also agreed to amend the proposed indication in the restriction wording from ‘Proliferative diabetic retinopathy without diabetic macular oedema’ to ‘Proliferative diabetic retinopathy’ in order to allow patients who develop DMO while on treatment with ranibizumab, to continue therapy accordingly.
- 7.5 The PBAC also recommended the restriction be further modified to allow the prescribing ophthalmologist or accredited ophthalmology registrar, in consultation with an ophthalmologist, to diagnose PDR using fluorescein angiography, or retinal photography, or optical coherence tomography (OCT).
- 7.6 The PBAC expressed a view that the recommended PDR PBS listing and the current DMO PBS listing for ranibizumab could potentially be amalgamated to simplify care for patients and requested the Department review the feasibility of such a change.
- 7.7 The PBAC accepted PRP was the appropriate comparator. The PBAC noted that ranibizumab and PRP were not mutually exclusive modalities, with different stages of the disease requiring different approaches including where a patient may be treated with ranibizumab prior or subsequent to PRP treatment. The PBAC noted treatment switching was evident in the presented clinical evidence, where patients switched between ranibizumab and PRP at the discretion of the lead investigator.
- 7.8 The PBAC noted the clinical evidence for ranibizumab was based on 2 head-to-head randomised trials comparing ranibizumab to PRP: the PRIDE trial and the Protocol S trial. The Protocol S trial included 305 PDR patients (394 eyes) with or without DMO over a 60-month period, assessing changes in BCVA, visual acuity of $\geq 10/15$ letters gains or loss, and the risk of developing DMO. The PRIDE trial focused specifically on

Public Summary Document – May 2025 PBAC Meeting

- 106 PDR patients without DMO over 24 months, measuring BCVA, changes in NV, and visual acuity of $\geq 5/10/15$ letters gains or loss. The PBAC noted the clinical trials included the whole population approved by the TGA and recommended for PBS listing, compared to the sponsor proposal that limited the population, presented as a sub-set, of the available evidence.
- 7.9 The PBAC noted that while ranibizumab showed early improvements in BCVA, these benefits were not consistently clinically meaningful or sustained long-term (see Table 8). The PBAC further noted the high rate of cross over from PRP to ranibizumab in the clinical trials created uncertainty in the magnitude of benefit (see paragraph 6.14). The PBAC considered that some improvement in BCVA may be supported, however it was noted that visual improvement was not the main goal of treatment in PDR, but rather the prevention of further visual loss, and as such a MCID for BCVA in the PDR population was difficult to define. The PBAC considered improvements in NV (Table 12), prevention of DMO (Table 11) and reduced need for vitrectomy surgery (paragraph 6.30 and Table 14) were all important outcomes with meaningful improvements based on the trials presented. The PBAC considered the claim of superior comparative effectiveness was supported for change in NV and risk of DMO and was uncertain but reasonable for improvement in visual acuity.
- 7.10 The PBAC considered that the safety profiles of ranibizumab and PRP were well understood, and the claim of non-inferior comparative safety was reasonable. The PBAC noted treatment with ranibizumab compared to PRP lead to a reduction in the requirement for vitrectomy.
- 7.11 The PBAC considered the cost utility analysis, using a 26-health state Markov model (plus a death state) of ranibizumab compared to PRP, was a reasonable approach. The PBAC noted the ESC raised a number of issues related to the model assumptions and the pre-PBAC response provided additional sensitivity analyses as well a substantial price reduction to address these uncertainties (see paragraphs 6.57 to 0). The PBAC considered the inclusion of treatment waning for DMO reduction, with the price reduction equivalent to the current effective price for DMO and sensitivity analysis exploring the removal of the treatment effect of improvement in BCVA, mitigated several economic uncertainties in the economic model and resulted in acceptable ICERs (see Table 10 and Table 11).
- 7.12 The PBAC noted the revised estimates from the pre-PBAC, inclusive of the expanded population of PDR with or without DMO (see Table 27). The PBAC noted there is a low risk that ranibizumab will be used in populations beyond the eligible population. As the PBAC has recommended a broader population than requested, the DUSC Secretariat will review the revised financial estimates.
- 7.13 The PBAC recommended an amendment to the written authority level of ranibizumab for Proliferative diabetic retinopathy (PDR) and/or Diabetic Macular Oedema (DMO), to Authority Required (Telephone/Electronic), for the initial treatment phase. The

Public Summary Document – May 2025 PBAC Meeting

PBAC also recommended an amendment to the written authority levels of aflibercept, dexamethasone implant and faricimab for Diabetic Macular oedema (DMO) to Authority Required (Telephone/Electronic) for all initial treatment phases.

- 7.14 The PBAC advised that ranibizumab is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC considered the Early Supply Rule should not apply to ranibizumab.
- 7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for ranibizumab:
- The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, and reduction in vitrectomy surgeries, over PRP;
 - The treatment is not expected to address a high and urgent unmet clinical need because an alternative therapy (PRP) is available;
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Restriction to be finalised.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.