An addendum to this Public Summary Document has been included at the end of the document.

5.13 RANIBIZUMAB, Solution for ocular implant 39.5 mg in 0.395 mL, Susvimo®, Roche Products Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required listing for ranibizumab delivered via port delivery system (herein identified as ranibizumab PDS), for the treatment of neovascular age-related macular degeneration (nAMD) in patients who have previously demonstrated a response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment.

1.2 Concurrent submissions were lodged to the Prostheses List Advisory Committee (PLAC) and the Medicare Services Advisory Committee (MSAC), seeking listing on the Prostheses List for the ocular implant and MBS reimbursement for clinicians performing the procedures associated with the port delivery system.

1.3 Listing was requested on the basis of a cost-minimisation approach versus intravitreal ranibizumab injection (herein identified as intravitreal ranibizumab).

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

Component	Description
Population	Patients with nAMD previously responsive to prior anti-VEGF treatment.
Intervention	Ranibizumab 100 mg/mL [a] (via the port delivery system); refill and exchange procedure occurring every 24 weeks.
Comparator	Ranibizumab 10 mg/mL[b] (via intravitreal injection), as a proxy for standard of care. Current algorithms suggest initiating treatment with a 4-weekly interval, and then attempting to treat and extend the treatment interval once response has been achieved.
Outcomes	BCVA; adverse events.
Clinical claim	Ranibizumab 100 mg/mL [a] via the port delivery system is noninferior in terms of maintaining BCVA (with a reduction in frequency visits for treatment administration), has manageable short-term safety related to the ocular implant procedure, and is noninferior in terms of long-term safety compared to ranibizumab 10 mg/mL[b] via intravitreal injections.

BCVA = best corrected visual acuity; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.
Source: Table 1.1, p.3 of the submission.
[a] 39.5 mg/0.395 mL injection, 0.395 mL vial.
[b] 2.3 mg/0.23 mL injection, 0.23 mL vial, and 1.65 mg/0.165 mL injection, 0.165 mL syringe are currently PBS-listed.

2 Background

Registration status

2.1 **TGA status at the time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of the PBAC meeting, the Round 1 Clinical Evaluation Report was available, but the Delegate's Overview was not available. The

PBAC considered that the Delegate's Overview would be informative for its decision, particularly with respect to the safety profile of the drug.

2.2 The initial proposed TGA indication for ranibizumab PDS was for the treatment of adult patients with neovascular (wet) AMD. This was consistent with the TGA indication for the main comparator, intravitreal ranibizumab, and other intravitreal anti-VEGF therapies. The TGA Clinical Evaluation Report Round 1 recommended that the indication should be treatment of adult patients with neovascular (wet) AMD who have previously responded to VEGF inhibitors. The TGA Clinical Evaluation Report also recommended the inclusion of a black box warning regarding device-related adverse events.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The PBAC noted that these were not finalised restrictions, and would require further revisions.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty (packs)**	**Max. qty (units)**	**№. of repeats**	**Proprietary name and manufacturer**
RANIBIZUMAB 39.5 mg/0.395 mL solution for ocular implant, 0.395 mL vial	NEW	1	1	0	Susvimo Roche Products Pty Ltd
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction Level / Method: ☒*Authority Required – In Writing* ☒~~Authority Required – Telephone/Electronic/Emergency~~				
	~~**Condition**~~ ***Indication:*** Subfoveal choroidal neovascularisation (CNV)				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be due to age-related macular degeneration (AMD)				
	AND				
	Clinical criteria:				
	The condition must have been previously diagnosed by optical coherence tomography; or				
	The condition must have been previously diagnosed by fluorescein angiography				
	AND				
	Clinical criteria:				
	~~The condition must have previously responded to anti-VEGF treatment~~ *Patient must have received PBS-subsidised treatment with ranibizumab or aflibercept for this condition*				
	AND				
	Clinical criteria:				
	The condition must be stable at the discretion of the treating physician				
	AND				

	~~**Clinical criteria:**~~
	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
	~~**AND**~~
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Prescribing Instructions: *Authority approval for initial treatment of each eye must be sought*
	Prescribing Instructions: *Authority approval for initial treatment of each eye must be sought.* *The first authority application for each eye must be made in writing.* *A written application must include:* *a) a completed authority prescription form; and* *b) a completed Subfoveal Choroidal Neovascularisation (CNV) Application Form.*
	~~**Administrative Advice:**~~ ~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ***Administrative Advice:*** *Any queries concerning the arrangements to prescribe may be directed to the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Where both eyes are affected by the condition, a quantity of 2 units can be requested on the same authority prescription form
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye
	~~**Administrative Advice:**~~ ~~Ranibizumab (Susvimo®) is intended for continuous delivery via the implant only. Do not administer by any other route (e.g., not as a bolus intravitreal injection)~~
	Administrative Advice: Ranibizumab 0.395 mL injection vial is not interchangeable with ranibizumab 0.165 mL injection syringe or ranibizumab 0.23 mL injection vial
	Administrative Advice: Special Pricing Arrangements apply

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats	Proprietary name and manufacturer
RANIBIZUMAB 39.5 mg/0.395 mL solution for ocular implant, 0.395 mL vial	NEW	1	1	0	Susvimo Roche Products Pty Ltd
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction Level / Method: ☒Authority Required – Telephone/Electronic/Emergency				
	Indication: *Subfoveal choroidal neovascularisation (CNV)*				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	The condition must be due to age-related macular degeneration (AMD)				
	AND				
	~~**Clinical criteria:**~~				
	~~The treatment must be the sole PBS-subsidised therapy for this condition~~				
	~~**AND**~~				
	Clinical criteria:				
	Patient must have previously been granted an authority prescription for the same eye				
	AND				
	Treatment criteria:				
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist				
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*				
	Administrative Advice: No increase in the maximum number of repeats may be authorised				
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	Administrative Advice: Ranibizumab 0.395mL injection vial is not interchangeable with ranibizumab 0.165 mL injection syringe or ranibizumab 0.23 mL injection vial				
	Administrative Advice: Special Pricing Arrangements apply				

3.2 The submission requested a maximum quantity of one ocular implant refill, with no repeats, which would provide approximately six months of therapy (the recommended treatment refill interval is 24 weeks). The manner of administration is via ocular implant (port delivery system).

3.3 The submission requested a special pricing arrangement (SPA) and a published DPMQ of $3212.28, although an effective price was not proposed. The sponsor stated that

the effective price may be calculated based on the effective price of intravitreal ranibizumab once a positive recommendation has been achieved for ranibizumab PDS.

3.4 The requested restriction proposed that ranibizumab PDS be reimbursed for patients with nAMD who have previously responded to intravitreal anti-VEGF treatment. The ARCHWAY trial randomised patients to ranibizumab PDS after they had been stabilised on anti-VEGF therapy, including at least 1 injection with intravitreal ranibizumab. In the 9 months prior to first study treatment, the median number of intravitreal ranibizumab injections in the study eye was 4.0 in the PDS arm and 4.0 in the intravitreal arm (mean 3.5 in the PDS 100 mg/mL arm and 3.8 in the intravitreal arm). Aflibercept had been administered to 11.3-12.0% of patients (mean of 0.4/0.3 in PDS/intravitreal arm). 16-19% had received 1 intravitreal ranibizumab injection. The ESC considered the trial evidence most strongly supports ranibizumab PDS use after previous stabilised response to intravitreal ranibizumab.

3.5 The PBAC agreed with the ESC that brolucizumab should not be allowed as a prior therapy, as it is listed on the PBS as a second-line treatment after patients have not responded sufficiently to aflibercept and/or ranibizumab.

3.6 The proposed restriction specified that response to anti-VEGF therapy must have previously been achieved, but response was not specifically defined. The ESC considered this may be reasonable as response could be determined according to discretion of the treating physician. The submission stated that clinician opinion suggested that patients may become eligible after 6-12 months of intravitreal anti-VEGF therapy. The ESC noted that the current brolucizumab restriction requires patients to have been insufficiently responsive to therapy despite at least 6 months treatment with aflibercept and/or ranibizumab. As such, the PBAC considered that a minimum treatment duration of prior intravitreal therapy of 6 months may be clinically appropriate in order to define a stabilised patient, and that this could be specified in the ranibizumab PDS listing.

3.7 The PBAC noted that the pivotal ARCHWAY trial required patients to receive at least 1 intravitreal ranibizumab injection prior to PDS implantation and considered it may potentially be clinically appropriate to have such a requirement in the PBS listing. The pre-PBAC response argued that, since aflibercept and ranibizumab are considered noninferior in efficacy and safety, intravitreal ranibizumab can be considered representative of available anti-VEGF therapies.

3.8 The submission noted that, if ranibizumab PDS is recommended, changes may be required to the PBS listings of intravitreal ranibizumab to allow supplemental dosing with intravitreal ranibizumab in between the fixed six-monthly intervals of ranibizumab PDS. The ESC noted that this may be inconsistent with the clinical criterion requested in the submission for all treatment phases: “The treatment must be the sole PBS-subsidised therapy for this condition.” The PBAC agreed with the ESC that supplementary intravitreal ranibizumab should be permitted, but also considered that clinicians may instead seek to shorten the duration between ranibizumab PDS

implant refill-exchanges if therapeutic efficacy showed signs of waning. The PBAC noted the Secretariat would provide further suggestions regarding the structure of any flow-on changes required for the PBS restriction for intravitreal ranibizumab.

3.9 The submission justified the initial telephone authority by stating that the evidence substantiating appropriateness for anti-VEGF therapy would have previously been provided. An initial written authority listing would be consistent with the existing ranibizumab, aflibercept and brolucizumab PBS listings. The ESC considered that in light of the November 2021 recommendation for continuing phase listings of aflibercept and ranibizumab to become Authority Required (STREAMLINED), it may also be appropriate to change the ranibizumab PDS continuing listing to be Authority Required (STREAMLINED) when the November 2021 recommendations are implemented.

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

4 Population and disease

4.1 Age-related macular degeneration is a chronic eye disease characterised by progressive degenerative abnormalities in the central retina (macula). Neovascular (wet) AMD (nAMD) occurs in around 10-15% of overall AMD cases and is characterised by choroidal neovascularisation, a process in which new blood vessels grow beneath the retina and macula. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, which contribute to the progression of the neovascular form of AMD. High levels of VEGF initiate the formation of new vessels (Wykoff 2018), which may leak fluid or blood and penetrate the photoreceptor layer, resulting in focal retinal detachment and rapid central vision loss (Bhutto 2012; van Lookeren Campagne 2014), and potential blindness (Wong 2014). If left untreated, nAMD eventually leads to irreversible vision loss and blindness.

4.2 Anti-VEGF medication can block the activity of the VEGF protein, which is predominantly responsible for the abnormal growth of blood vessels and fluid leakage under the retina, thereby stopping the growth of abnormal blood vessels and fluid leakage. Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to all biologically active VEGF-A isoforms, thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Currently, treatment is initiated with one intravitreal injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity; that is, no change in visual acuity and in other signs and symptoms of the disease under continued treatment.

4.3 The proposed clinical management algorithm positioned ranibizumab PDS as an alternative treatment option for patients who have responded to standard of care intravitreal injections, and who are willing to undergo treatment with a preference for the longest available treatment interval. The population described in the submission

includes both patients on a four-weekly treatment schedule, who are unable to extend to less frequent intervals (four-weekly population), and patients who may be on treat-and-extend (T&E) regimens but who would prefer treatment with ranibizumab PDS in order to reduce treatment burden (patient preference population). The submission noted that clinicians have suggested that a maximum of 20% of patients in totality meet one or more of these criteria, and that the majority of this group would be frequent injection users with 75% of these patients electing therapy. The Pre-Sub-Committee Response (PSCR) provided additional clinician feedback on the clinical need for ranibizumab PDS. The ESC noted limited details about how this feedback was solicited and that 15% (75%x20%) uptake appeared poorly justified but considered it may be reasonable to assume that the majority of use would be in those with higher treatment burden.

4.4 This submission was for a vial of 0.395 mL containing 39.5 mg of ranibizumab at a concentration of 100 mg/mL, which is intended for injection via the ocular implant. The implant is a refillable drug reservoir that is inserted into the eye through the *pars plana*, and secured within the scleral incision, with an extrascleral flange remaining visible through the conjunctiva following insertion. Once filled with ranibizumab 100 mg/mL, the implant is designed to provide continuous release of drug into the eye. The implant can be refilled via a refill-exchange procedure, which requires a specific needle that allows implant contents to be extracted simultaneously as the implant is filled with replacement ranibizumab.

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

5 Comparator

5.1 The submission appropriately nominated standard of care, ranibizumab (delivered via intravitreal injection) as the main comparator, on the basis of being the same active ingredient as the therapy proposed for listing on the PBS, with the same pharmacological action and in the same therapeutic class.

5.2 The PBAC agreed with the submission that intravitreal ranibizumab can be considered representative of either intravitreal ranibizumab or aflibercept in terms of the appropriate comparator, as the PBAC has previously accepted noninferiority between the two agents, priced on an injection:injection basis (Therapeutic Relativity Sheets, Ophthalmologicals).

5.3 Usual dosing of intravitreal ranibizumab for the treatment of wet AMD is 0.5 mg by intravitreal injection every month for three injections, with scheduled or variable treatment thereafter.

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 health care professionals (HCPs) (3) and an organisation via the Consumer Comments facility on the PBS website.

6.3 The comments from the HCPs described the benefits of treatment with ranibizumab PDS, particularly around the decreased burden of treatment for patients and carers, and improved compliance and anticipated associated long-term outcomes. However, 2 HCPs acknowledged disadvantages of ranibizumab PDS in terms of surgical risks associated with the implant and patient fear of surgery, and 1 HCP noted the short-term complications with ranibizumab PDS including endophthalmitis, and unknown long-term complications.

6.4 The PBAC noted the advice received from the Macular Disease Foundation Australia (MDFA). The MDFA stated that several groups of patients will receive the greatest benefit from access to ranibizumab PDS, specifically patients who are unable to extend the intervals of anti-VEGF injections and experience treatment fatigue, those who require treatment in both eyes but cannot receive same-day intravitreal injections, and patients in aged care facilities or those otherwise at risk of missing appointments. The MDFA stated that only about 50% of patients continue to receive current treatments beyond 5 years, and that addressing the issue of long-term adherence and persistence is anticipated to ensure more patients with nAMD avoid unnecessary severe vision loss and blindness. The MDFA acknowledged that ranibizumab PDS will not be appropriate for all patients, as the implantation necessitates a significant surgical procedure, and will require frequent check-ups within the first 3 months after surgery and potentially every 2-3 months thereafter for at least the first year. The PBAC noted that the advice from the MDFA was, overall, supportive of the evidence provided in the submission.

Clinical trial

6.5 The submission was based on one head-to-head randomised noninferiority trial comparing ranibizumab PDS (including device implantation and refill-exchange procedures) with intravitreal ranibizumab (ARCHWAY).

6.6 Details of the ARCHWAY trial are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ARCHWAY NCT03677934	Primary CSR Study GR40548, (Archway): A Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration.	October, 2020
	Holekamp, N. M., Campochiaro P. A., Chang, M. A. et al. Archway Randomized Phase 3 Trial of the Port Delivery System With Ranibizumab for Neovascular Age-Related Macular Degeneration.	*Ophthalmology*, 2021; doi:10.1016/j.ophtha.2021.09.016

Source: Table 2.3, p.37 of the submission

The key features of the ARCHWAY trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
ARCHWAY	418	Randomised, multicentre, active comparator controlled, 40 weeks	Unclear	nAMD which previously responded to anti-VEGF treatment	Change from baseline in BCVA score; adverse events

BCVA = best corrected visual acuity; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.
Source: Table 2.7, p.42; Table 2.11, p.46; Table 2.12, p.47 of the submission

6.7 The ARCHWAY trial compared treatment with ranibizumab PDS to treatment with intravitreal ranibizumab administered once every four weeks (Q4W), in patients who had previously responded to intravitreal anti-VEGF therapy. The PDS was filled prior to implantation with approximately 20 µL of 100 mg/mL ranibizumab and surgically inserted in the study eye of patients in the ranibizumab PDS arm. After the initial fill of the implant with ranibizumab, patients received implant refill-exchanges at fixed 24-week intervals (with approximately 20 µL of ranibizumab in the implant after refill-exchange).

6.8 The dosing regimen for intravitreal ranibizumab in the ARCHWAY trial (Q4W) did not allow T&E dosing to increase the intervals between injections, which is a standard treatment practice for anti-VEGF therapies in Australian patients and is intended to maintain the same patient benefit while subjecting the patient to fewer injections. In Australia, anti-VEGF therapies are initially administered Q4W, and can be continued as either fixed (e.g. monthly) or variable (T&E) dosing regimens, where the interval may be extended stepwise until signs of disease activity or visual impairment recur.

6.9 Eligible patients for the ARCHWAY trial were required to have an initial diagnosis of nAMD within 9 months prior to screening, and to have received previous treatment with at least 3 anti-VEGF intravitreal injections within 6 months prior to the screening visit. If a patient had not received at least 3 anti-VEGF injections but was otherwise eligible for the study, the patient could be treated in a run-in phase to meet this specific criterion. Further, at the screening visit, patients received an additional intravitreal injection of 0.5 mg ranibizumab if they received only 3 doses of anti-VEGF intravitreal agents within the last 6 months and/or if the last treatment received prior to screening was not 0.5 mg ranibizumab.

6.10 Response to anti-VEGF treatment was assessed via overall decrease in nAMD disease activity detected on optical coherence tomography (OCT), and stable or improved best

corrected visual acuity (BCVA). Outcomes in patients with longer-term disease who may have received years of anti-VEGF therapy have not yet been evaluated. The study was an open-label design, given the nature of the therapies being compared, although the visual assessors conducting outcome measurements were blinded to treatment assignment. The study was therefore considered to be of an unclear risk of bias overall.

6.11 According to the PDS device instructions for use, the implant is designed to remain in place for the remainder of a patient's lifespan unless contraindicated or some other reason for explantation arises. The primary outcome assessment in ARCHWAY was conducted at week 36-40, a duration which included only 1 full 24-week refill-exchange period. The long-term safety and effectiveness of ranibizumab PDS are yet to be fully assessed. The PSCR provided data to 96 weeks, comprising three full refill-exchange periods, which was supportive of ranibizumab PDS efficacy (see Table 4). There is also an ongoing open-label extension study designed to evaluate the long-term safety and tolerability of ranibizumab PDS in patients with nAMD (PORTAL; NCT03683251; completion scheduled for 2026).

6.12 In the ranibizumab PDS treatment arm, supplementary treatment with intravitreal ranibizumab was allowed in the study protocol, based on central subfield thickness (CST) and best corrected visual acuity (BCVA). Of the patients assessed, 5.2% (13/241) received supplemental treatment (4 patients received two supplemental treatments and the remainder received 1 supplemental treatment). Of the 13 patients requiring supplemental treatment, the reasons were due to the BCVA decrease criteria being met (2 patients), the CST increase criteria being met (7 patients), or the BCVA/CST combined criteria being met (4 patients). It is not certain how many patients would qualify for supplementary treatment in Australian clinical practice.

6.13 A noninferiority margin of -4.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters was applied in the submission, which was consistent with the noninferiority margin used in the ARCHWAY trial. In the ARCHWAY publication (Holekamp et al., 2021), the noninferiority margin appeared to be based on a reference stating that a change of 5 in the score between examinations approximates a 1-line change, which for eyes with acuity better than 20/100 has a high probability (~90% or higher) of being a real change in visual acuity and not a difference due to chance (Beck et al., 2007). The primary outcome in the ARCHWAY trial, and in the submission, was change from baseline in BCVA using the EDTRS chart. This aligns with previous MSAC conclusions on visual acuity being the preferred outcome measure for assessing ocular disease activity (Section 2, Optical coherence tomography Public Summary Document [PSD], July 2015 MSAC meeting), as well as previous PBAC deliberations. A noninferiority margin of -3.9 letters was used for the assessment of a secondary endpoint of change from baseline in BCVA in the ARCHWAY trial. This was associated with advice from the European Medicines Agency in September 2019 that a noninferiority margin of 3-4 letters was recommended, as -4.5 letters is very close to the 5 letter threshold that is considered a real change in visual acuity and clinically

meaningful for an individual patient (Beck et al. 2007). The PBAC has previously accepted that an improvement in visual acuity of 10 letters represented a clinically important result, although noted that an increase of 5 or more BCVA letters might represent a clinically important difference for some patients and the clinical importance will also depend on the baseline visual acuity of each eye (ranibizumab PSD, March 2013 PBAC Meeting). Patients with well-preserved vision at baseline may experience a less clinically meaningful outcome than those patients with poorer vision at baseline. A noninferiority margin of 4 letters (paragraph 6.11, brolucizumab PSD, November 2019 PBAC meeting) has recently been accepted by the PBAC for the treatment of patients with subfoveal choroidal neovascularisation (CNV).

6.14 The submission claimed that ranibizumab PDS is likely to reduce the overall treatment and monitoring burden in clinical practice while maintaining visual acuity gains in nAMD. However, in the ARCHWAY trial patients in both treatment arms attended monthly appointments, so the ranibizumab PDS arm aligned with the visit schedule of the monthly intravitreal ranibizumab comparator arm, in order to maintain visual acuity examiner masking and reduce the risk of ascertainment bias. The number of monitoring visits, and in particular the frequency of monitoring required to address potential adverse events as early as possible, is yet to be determined. The PBAC agreed with the ESC that, while ranibizumab PDS requires fewer refills compared to the number of intravitreal ranibizumab injections, thus reducing the overall injection burden, it does not follow that monitoring costs will be decreased, and they will likely be increased in the initial stages of treatment, given the risks associated with the surgical procedure.

Comparative effectiveness

6.15 The results for the primary outcome, change in BCVA score from baseline averaged over Week 36 and Week 40, and the secondary outcome, change in BCVA score averaged over Week 44 and Week 48, are summarised in Table 4. The table also includes final results at Week 88/92, which were provided with the PSCR and not evaluated.

Table 4: Results of change in BCVA score from baseline (ARCHWAY)

	Ranibizumab PDS (N = 248)	Intravitreal ranibizumab (N = 167)	Difference between adjusted means (95% CI)
Change to average of Week 36 and Week 40	0.2 (-0.7, 1.1)	0.5 (-0.6, 1.6)	-0.3 (-1.7, 1.1)
Change to average of Week 44 and Week 48	0.0 (-1.0, 1.0)	0.2 (-1.0, 1.4)	-0.2 (-1.8, 1.3)
Change to average of Week 88 and Week 92	-1.1 (-2.3, 0.1)	-0.5 (-2.0, 1.0)	-0.6 (-2.5, 1.3)

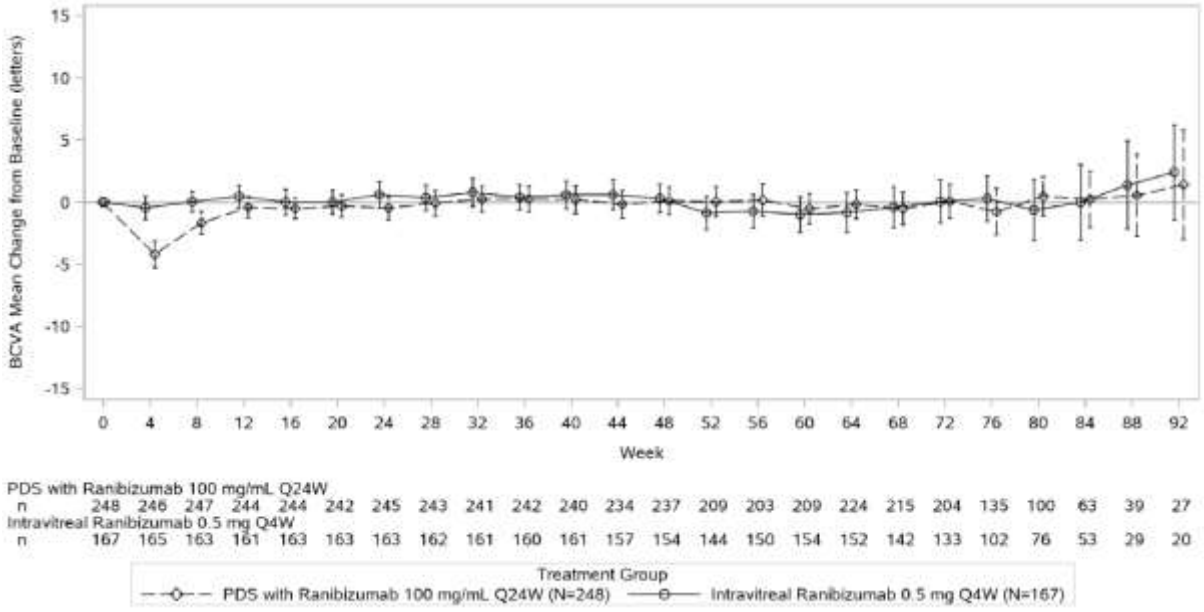
PDS = port delivery system.
Source: Table 2.14, p.52; Table 2.15, p.53 of the submission; Table 5, p.26 of Final ARCHWAY CSR, provided with PSCR.

6.16 The lower limit of the 95% confidence interval (CI) of the difference in adjusted means at the average of Week 36 and Week 40 was -1.7 ETDRS letters, thereby meeting the pre-specified noninferiority margin of ± 4.5 letters. The mean change in BCVA score

from baseline averaged over Week 36 and Week 40 appeared to be maintained when averaged over Week 44 and Week 48, with the lower limit of the 95% CI of the difference in adjusted means at the average over this time period being -1.8 ETDRS letters.

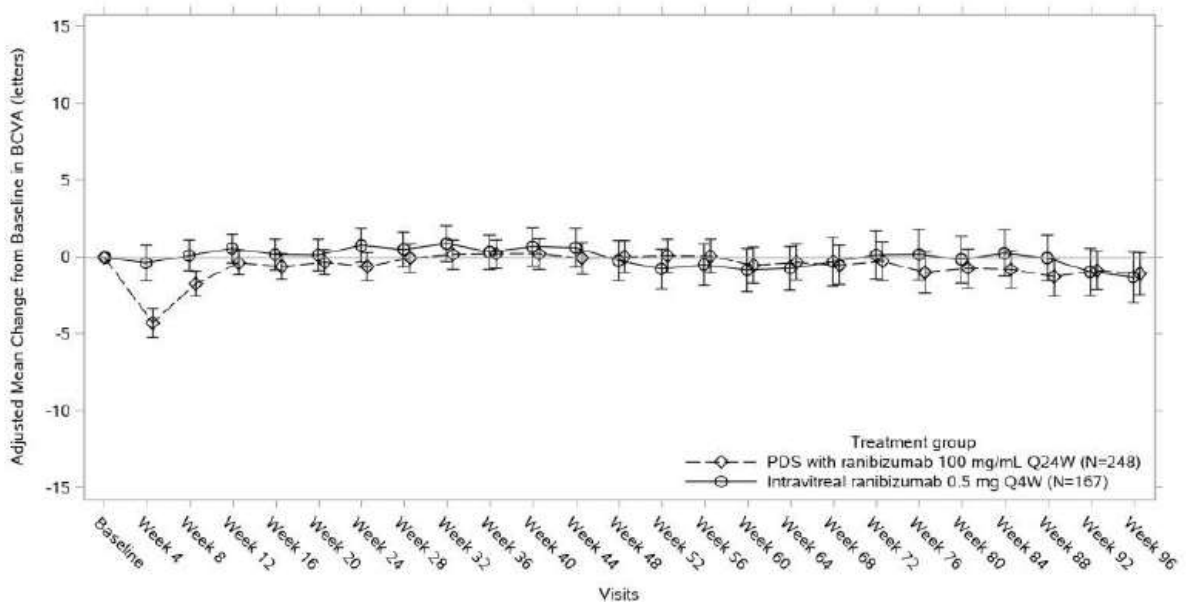
6.17 The mean change from baseline in BCVA score over time (assessed every four weeks starting from day 1) is summarised in Figure 1. Updated data to week 96 was presented in the PSCR, and is shown in Figure 2.

Figure 1: Mean change from baseline in BCVA score in study eye over time



Source: Figure 2.3, p.53 of the submission
Abbreviations: BCVA, best corrected visual acuity; PDS, port delivery system; Q4W, once every four weeks; Q24W, once every 24 weeks

Figure 2: Adjusted mean change in best corrected visual acuity over time (observed data)



Source: Final ARCHWAY CSR (Figure 3); presented on p6 of the PSCR.
Abbreviations: BCVA=best corrected visual acuity; Q4W=every four weeks; Q24W=every 24 weeks

6.18 The results for mean change from baseline in BCVA score over time suggest that there is an initial worsening in BCVA of approximately 5 ETDRS letters associated with the surgical procedure required for the port delivery system implant, which resolves after approximately 12 weeks. Although the submission stated that this was not a clinically meaningful change, the ESC agreed with the evaluation that a difference of 5 letters on ETDRS may be considered noticeable by patients according to Beck et al. (2007) and may be clinically meaningful. The clinical relevance of this change would also depend upon the baseline visual acuity; in the ARCHWAY study, visual acuity at baseline (mean = 74.8 letters) already represented an improvement in response to anti-VEGF medicine. Additionally, as the value of 5 is an average on a scale measure, a proportion of patients will experience more severe worsening following device implantation, which may require some lifestyle adjustment by patients until this resolves. The TGA Clinical Evaluator's report suggested adding a special warning regarding postoperative reduced visual acuity in the PI. Following the resolution of this initial worsening, change from baseline in BCVA appears to be maintained, with similar results for both the port delivery system and intravitreal treatment arms for the duration of the study.

6.19 The proportion of patients in the ranibizumab PDS arm who required supplementary treatment with intravitreal ranibizumab is summarised in Table 5.

Table 5: Proportion of patients in the ranibizumab PDS arm requiring supplementary treatment with intravitreal ranibizumab

	Ranibizumab PDS, n (%) (N=248)
Patients assessed prior to first refill-exchange (baseline through to Week 24)	246 (99.1)
Received 1–2 supplemental treatments[a,b,c]	4 (1.6)
Patients assessed prior to second refill-exchange (baseline through to Week 48)	241 (97.2)
Received 1–2 supplemental treatments[b,d]	13 (5.2)

PDS = port delivery system.
Source: Table 2.19, p.58 of the submission
Analysis is based on the mixed-effect repeated measures (MMRM) method based on treatment policy estimates
[a] Three of the four patients received supplemental treatment in error
[b] Number of patients assessed as denominator
[c] One patient received two supplemental treatments and three patients received one supplemental treatment
[d] Four patients received two supplemental treatments and nine patients received one supplemental treatment

6.20 A high proportion of patients maintained disease control without the need for supplementary treatment. In the period to the second refill-exchange (Week 48), 5.2% of patients required supplemental intravitreal ranibizumab. At Week 96, 31/246 patients (12.6%) received at least one supplemental treatment; of the 31 patients, 18 (58.1%) received only one supplement treatment.

6.21 Treatment preference was measured using the Port Delivery System Patient Preference Questionnaire (PPPQ). The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference and the reasons for their preference.

6.22 After Week 40, 218 of 234 patients (93.2%) in the ranibizumab PDS arm reported preferring continuous delivery of ranibizumab PDS over ranibizumab intravitreal injections. The most common reason cited was 'fewer treatments' (175/218). Three of 234 patients (1.3%) preferred ranibizumab intravitreal injections, with the reason provided being 'requires less time for treatment' (1/3) or 'other reason' (2/3). Thirteen patients (5.6%) had no preference for either route of administration. The PPPQ was modified for use with the ranibizumab PDS and tested and validated in the phase II LADDER clinical trial. However, it has not been more broadly used or validated beyond this, and may not capture all potential benefits of the comparator since patients in the intravitreal ranibizumab arm were not surveyed. Few patients in the ranibizumab PDS arm (12/428 = 5%) completed the questionnaire.

6.23 Results for the Macular Disease Treatment Satisfaction Questionnaire (MacTSQ), designed to measure satisfaction with treatment for macular disease including late-onset macular degeneration, suggested no difference between groups in terms of impact of treatment, or information provision and convenience.

Comparative harms

6.24 The incidence of adverse events reported in the ARCHWAY trial, both before and after the 40-week assessment point, are summarised in Table 6. Final trial results were provided with the PSCR, but these were not evaluated.

Table 6: Summary of adverse events in the ARCHWAY trial (safety population)

	Ranibizumab PDS, n (%) (N = 248)		Intravitreal ranibizumab, n (%) (N = 167)	
	Up to week 40[a]	After week 40[b]	Up to week 40[a]	After week 40[b]
Patients with ≥1 adverse event	243 (98.0)	179 (71.0)	114 (68.3)	105 (62.9)
Ocular adverse events: study eye				
Patients with ≥1 adverse event	234 (94.4)	78 (31.5)	59 (35.3)	45 (26.9)
Patients with ≥1 adverse event leading to withdrawal from treatment	5 (2.0)	3 (1.2)	0	1 (0.6)
Patients with ≥1 serious adverse event	14 (5.6)	7 (2.8)	2 (1.2)	2 (1.2)
Total number of deaths	2 (0.8)	3 (1.2)	1 (0.6)	2 (1.2)

PDS = port delivery system.
Source: Table 2.21, p.62 of the submission.
[a] Includes events with onset up to 294 days (42 weeks) post first study treatment.
[b] All data from Week 40 (includes events with onset after 294 days [42 weeks] post first study treatment) through 11 September 2020 clinical cut off date.

6.25 Adverse events and ocular adverse events were higher in the ranibizumab PDS arm compared with the intravitreal ranibizumab arm. This difference was higher before the 40-week assessment but persisted for the duration of the study period. At Week 96, ranibizumab PDS was associated with a higher incidence of ocular adverse events compared to intravitreal ranibizumab (97.6% versus 52.1%). This difference was higher in the initial post-operative period (within 37 days of implantation; 91.9% versus 10.8%); the PSCR stated that the difference between treatments at the subsequent time period to Week 96 was 60.5% versus 49.1%.

6.26 Three deaths were reported prior to Week 40, and from Week 40 through to the clinical cut-off date, five deaths were reported. Overall, no deaths were considered related to the implant (including implant, implant procedure, or initial fill needle), intravitreal injection, or study drug by the investigator.

6.27 Ocular adverse events thought to be caused by study treatment are summarised in Table 7. Results to Week 96 were provided with the PSCR in the Final ARCHWAY CSR.

Table 7: Summary of ocular adverse events suspected to be caused by study treatment in the ARCHWAY trial (safety population)

	Ranibizumab PDS, n (%) (N = 248)			Intravitreal ranibizumab, n (%) (N = 167)		
	Onset within 37 days[a]	Onset after 37 days[b]	Onset after Week 40[c]	Onset within 37 days[a]	Onset after 37 days[b]	Onset after Week 40[c]
Total number of patients with ≥1 adverse event caused by implant	218 (87.9)	27 (10.9)	12 (4.8)	NA	NA	NA
Total number of patients with ≥1 adverse event caused by refill	0	15 (6.0)	10 (4.0)	NA	NA	NA
Total number of patients with ≥1 adverse event caused by explant	0	2 (0.8)	3 (1.2)	NA	NA	NA
Total number of patients with ≥1 adverse event caused by ranibizumab[c]	57 (23.0)	12 (4.8)	5 (2.0)	2 (1.2)	8 (4.8)	5 (3.0)
Total number of patients with ≥1 adverse event caused by intravitreal injection procedure	0	1 (0.4)	3 (1.2)	11 (6.6)	15 (9.0)	22 (13.2)

NA = not applicable; PDS = port delivery system.
Source: Table 2.23, p.66 of the submission.
[a] Post first study treatment.
[b] All data from Week 40 (includes events with onset after 294 days [42 weeks] post first study treatment) through 11 September 2020 (clinical cut off date).
[c] Either PDS or intravitreal injection.

6.28 The most common ocular adverse events suspected by the investigator to be caused by the implant included anterior chamber cell or anterior chamber flare, cortical cataract, conjunctival bleb, conjunctival disorder, conjunctival haemorrhage, conjunctival oedema, corneal disorder, corneal oedema, eye pain or irritation, foreign body sensation in eye, hypotony of eye, implant site discolouration, iritis, vitreous haemorrhage, blurred vision or reduction in visual acuity, and scleral thinning.

6.29 Adverse events suspected by the investigator to be caused by the refill-exchange procedure included eye pain, anterior chamber cell, conjunctival bleb, and conjunctival haemorrhage. There was one device dislocation suspected by the investigator to be caused by refill-exchange.

6.30 In the intravitreal ranibizumab arm, the most common adverse events suspected by the investigator to be caused by the intravitreal injection procedure included conjunctival haemorrhage, eye irritation, eye pain, and blurred vision.

6.31 There were 4 implant removal procedures (explants) performed up to week 40, 3 because of an ocular adverse event (endophthalmitis, recurrent conjunctival retraction, and implant dislocation) and 1 because of a damaged implant. There were 3 additional removals performed from week 40 to the clinical cut-off date, due to drug hypersensitivity (one patient) and implant dislocations (two patients).

6.32 Up until week 40, there was one device dislocation which occurred during an unsuccessful refill-exchange procedure. From week 40 through to the clinical cut-off date, 2 patients experienced a device dislocation. These events were considered serious and severe. In all cases, dislocation was thought to be at least partly due to the

size of the incision made during the initial implant procedure (>3.7 mm in length). Current advice (Instructions for Use) has been updated from that provided during the trial to minimise the risk of implant dislocation occurring. Specifically, an incision length of 3.5 mm is now mandated (changed from previous guidance of 3.5 to 3.7 mm), sutures are to be placed for any final incisions greater than 3.5 mm, and laser should be applied only to the exposed *pars plana* without enlarging the scleral wound.

6.33 Serious ocular adverse events are summarised in Table 8 below, sourced from the Final ARCHWAY CSR provided with the PSCR.

Table 8: Summary of serious ocular adverse events in the ARCHWAY trial to clinical cut-off date (safety population)

	Ranibizumab PDS, n (%) (N = 248)	Intravitreal ranibizumab, n (%) (N = 167)
Total number of patients with ≥1 ocular serious adverse events	19 (7.7)	4 (2.4)
Conjunctival erosion	2 (0.8)	0
Rhegmatogenous retinal detachment	2 (0.8)	0
Visual acuity reduced	3 (1.2)	0
Visual impairment	2 (0.8)	0
Vitreous haemorrhage	2 (0.8)	1 (0.6)
Choroidal detachment	1 (0.4)	0
Necrotising retinitis	1 (0.4)	0
Retinal tear	1 (0.4)	1 (0.6)
Endophthalmitis	4 (1.6)	1 (0.6)
Conjunctival retraction	2 (0.8)	1 (0.6)
Device dislocation	3 (1.2)	0
Cataract cortical	1 (0.4)	0
Conjunctival bleb	1 (0.4)	0
Corneal disorder	1 (0.4)	0
Retinal pigment epithelial tear	1 (0.4)	0

PDS = port delivery system.
Source: Table 2.24, p.68 of the submission; ARCHWAY primary CSR Table 20, p.121; ARCHWAY update CSR Table 11, p.67

6.34 The incidence of serious ocular adverse events was higher in the ranibizumab PDS treatment arm compared with the intravitreal ranibizumab treatment arm. The most commonly reported ocular serious adverse events associated with the ranibizumab PDS were reduced visual acuity, endophthalmitis, and device dislocation. Most events in the port delivery system treatment arm were linked to the surgical nature of the intervention, and the technique used for the implant insertion procedure. The PSCR considered there was a low absolute number of adverse events and highlighted the comparability of these events to those seen in trials of other ocular surgical procedures, mainly involving glaucoma drainage device implants. The ESC advised that that the risks associated with the PDS may potentially be higher outside of the controlled trial setting.

Benefits/harms

6.35 A benefits/harms summary was not presented for ranibizumab PDS versus intravitreal ranibizumab due to the claim of noninferiority.

Clinical claim

6.36 The submission described ranibizumab PDS as noninferior in terms of efficacy compared with intravitreal ranibizumab in patients with nAMD who had previously responded to intravitreal anti-VEGF treatment, with manageable short-term safety related to the implant procedure and noninferior long-term safety compared to intravitreal ranibizumab. The ESC agreed with the evaluation that the claim of noninferiority may be reasonable for efficacy, but not for safety.

6.37 While the clinical claim of noninferior efficacy may be reasonable for ranibizumab PDS, the evaluation and the ESC raised applicability issues associated with the ARCHWAY trial design indicating that trial results may not necessarily be generalisable to the proposed Australian patient population:

- The number and types of prior anti-VEGF injections in the ARCHWAY trial may not reflect the population who would use the PDS in practice. The submission stated that patients may become eligible after 6-12 months of (any) intravitreal anti-VEGF therapy. Patients were treated for an average of 5.3-5.9 months prior to randomisation, with an average of 5.0 VEGF inhibitor intravitreal injections in both arms (the mean number of ranibizumab injections in the 9 months prior to first study treatment was 3.5 and 3.8, in the PDS and intravitreal arms, respectively). The evaluation considered that patients in the trial may not have been sufficiently stabilised before using the PDS if they had received only 3 prior injections, but the PSCR clarified that only 1 patient was in this group. The evaluation had also raised concerns that the ARCHWAY results may not be applicable to patients in the proposed Australian population if they had been using intravitreal therapy for longer than 9 months, as eligible patients in the trial were required to have an initial diagnosis within 9 months prior to screening. Overall, the PBAC considered that the effect of this issue could be minimised if patients were stabilised for a minimum of 6 months on prior treatment. The PBAC also considered that the clinical evidence more strongly supported use following stabilisation after ranibizumab than after aflibercept.
- Four-weekly injections of intravitreal ranibizumab in the control arm of ARCHWAY did not allow dosing to increase the intervals between injections, as would be seen in standard T&E Australian practice for part of the submission's proposed population. It was also unclear whether any patients in the trial had previously been stabilised on a T&E regimen. The submission maintained that as T&E regimens have been shown to be noninferior to Q4W regimens of intravitreal anti-VEGF medicines, any clinical claim made comparing ranibizumab PDS with Q4W intravitreal ranibizumab may reasonably be extended to T&E regimens. The PBAC had previously noted that, in Australian practice, the T&E regimen is expected and should apply to all anti-VEGF medicines and that there are no clinical reasons for dosing frequencies amongst them to be different to each other (paragraph 7.4 and 7.5, brolucizumab PSD, November 2019 PBAC meeting).

6.38 The safety profile for ranibizumab PDS included a greater risk of serious ocular adverse events including choroidal detachment, endophthalmitis, and vitreous haemorrhage compared with monthly intravitreal injections. Overall, the risks for serious adverse events were higher both during the post-surgical period and were ongoing after Week 40. Although these were largely manageable under tightly controlled trial conditions, it is unclear whether similar results would occur in the broader Australian PBS population. Further, patients with the implant appear to continue to be at risk for several adverse events even after the post-surgical period. Overall, the evaluation and the ESC considered there are significant safety risks associated with the port delivery system, which suggest it may have inferior safety when compared with intravitreal ranibizumab. The PSCR stated that the rate of adverse events should reduce with experience with the procedure and that amendments have been made to the instructions for use (for example, guidance on the length of the surgical incision). Further, the pre-PBAC response reiterated that there were few serious adverse events observed in ARCHWAY, which were consistent with those expected for a novel therapeutic involving ocular implantation surgery and refill procedures.

6.39 The PBAC considered that the clinical claim of noninferior effectiveness of ranibizumab PDS compared with intravitreal ranibizumab may be reasonable based on change from baseline in BCVA score, although there was an initial worsening in BVCA associated with the surgical procedure and a small proportion of patients treated with ranibizumab PDS required supplementary treatment with intravitreal ranibizumab in addition to the 24-weekly refill-exchange procedures. The additional data to Week 96 supplied with the PSCR provided further confidence in the noninferiority conclusion, although ultimately the long-term evidence would only be available with the PORTAL extension study.

6.40 The PBAC considered that the majority of the safety concerns associated with ranibizumab PDS were associated with the surgical procedure to implant the ocular device. The PBAC noted that the safety issues are being considered by the TGA, and it considered that a positive Delegate's Overview would be required to clarify the overall safety profile of the drug.

Economic analysis

6.41 The submission presented a cost-minimisation/cost comparison in patients who had previously responded to intravitreal anti-VEGF treatment based on the claim of noninferior efficacy and manageable safety of ranibizumab PDS compared with intravitreal ranibizumab.

6.42 The submission first calculated its proposed published ex-manufacturer price for ranibizumab PDS based on the published AEMP of intravitreal injection and assuming equi-effective doses of 2.17 PDS administrations per year and 7.09 intravitreal injections per year (Table 9). The submission then presented a cost-minimisation calculation including other cost consequences (Table 10), which changed the assumed equi-effective doses to 2.17 PDS administrations per year and 10.07 intravitreal

injections per year.

6.43 In these calculations, the estimated number of doses per year of ranibizumab PDS was based on use in the ARCHWAY trial (refill and exchange procedure every 24 weeks) and assuming perfect compliance (2.167=52/24 weeks). For the estimated number of doses per year of intravitreal ranibizumab in the cost-minimisation calculation, it was assumed that 50% of patients would have dosing consistent with the ARCHWAY trial (intravitreal injection every 28 days) and perfect compliance (13.04 doses per year=365.25/28 days); and 50% of patients would receive T&E dosing (7.09 intravitreal injections per year, based on the 2018 DUSC analysis of ranibizumab and aflibercept utilisation); resulting in 10.07 injections per patient per year. The 50-50% split was not justified. In the price calculation, the estimated number of doses per year of intravitreal ranibizumab (7.09) was based on the DUSC analysis. The submission noted that the number of injections informing the price calculation (7.09) was lower than the number of injections anticipated to be replaced in clinical practice (10.07) but did not provide further justification for this difference.

6.44 The population in the DUSC analysis included people on both Q4W and T&E regimens, and the submission's estimated number of intravitreal ranibizumab doses per year would therefore overestimate the average number of doses used by patients on T&E regimens only. If it is assumed that 100% of patients receiving intravitreal ranibizumab are dosed according to the DUSC analyses of ranibizumab and aflibercept utilisation, the equi-effective doses would be:

- 2.17 doses of ranibizumab PDS is equivalent to 7.09 injections of intravitreal ranibizumab annually (DUSC 2018 analysis).
- 2.17 doses of ranibizumab PDS is equivalent to 6.31 injections of intravitreal ranibizumab annually (updated DUSC Secretariat analysis).

6.45 The updated DUSC Secretariat analysis was based on patients who received intravitreal aflibercept and ranibizumab under AMD authority codes and initiated treatment in 2018. The analysis suggested that the average number of scripts per patient in their second year of treatment (as a proxy for stabilised patients) has decreased from 7.09 (for patients initiating treatment in 2015) to 6.31 (for patients initiating treatment in 2018).

6.46 Table 9 presents the submission's basis for calculating its proposed published price for ranibizumab PDS using the 2015 DUSC analysis (7.09 injections per year). The table also presents the evaluation's basis for the revised price based on the same approach but using the results of the updated DUSC Secretariat analysis (6.31 injections per year).

Table 9: Basis for the calculation of the proposed price for ranibizumab PDS over two years

		Intravitreal ranibizumab	Ranibizumab PDS	Source/calculation
SUBMISSION				
A	Ex-manufacturer price (published)	$932.40	$3,051.10	Intravitreal ranibizumab = ex-manufacturer price Ranibizumab PDS = C / B
B	Injections	7.09 × 2 = 14.18	2.167 × 2 = 4.334	Intravitreal ranibizumab = 7.09/year (DUSC analysis) Ranibizumab PDS = 2.167/year (ARCHWAY trial)
C	Drug cost over 2 years	$13,221.43	$13,221.43	Intravitreal ranibizumab = A × B Ranibizumab PDS = assumed equal to intravitreal ranibizumab
EVALUATION				
A	Ex-manufacturer price (published)	$932.40	$2,715.44	Intravitreal ranibizumab = ex-manufacturer price Ranibizumab PDS = C / B
B	Injections	6.31 × 2 = 12.62	2.167 × 2 = 4.334	Intravitreal ranibizumab = 6.31/year (updated DUSC Secretariat analysis) Ranibizumab PDS = 2.167/year (ARCHWAY trial)
C	Drug cost over 2 years	$11,766.89	$11,766.89	Intravitreal ranibizumab = A × B Ranibizumab PDS = assumed equal to intravitreal ranibizumab

PDS = port delivery system.
Source: 'Cost minimisation analysis' spreadsheet

6.47 Table 10 shows the cost-minimisation calculation as presented in the submission, seeking to establish that the cost per patient for ranibizumab PDS would be no more than the cost per patient of intravitreal ranibizumab. The submission's analysis included costs for the implant and the procedure of its implantation, drugs (based on DPMQ), administration, monitoring, supplemental intravitreal ranibizumab, adverse events and explantation. The published ranibizumab PDS DPMQ ($3,212.32) corresponds to the AEMP calculated using drug costs only ($3,051.10, see Table 9 above). Costs based on a revised analysis conducted during the evaluation, using drug costs based on the published AEMP, and assuming 2.17 doses of ranibizumab PDS is equivalent to 6.31 injections of intravitreal ranibizumab annually are also presented in the table below.

Table 10: Results of the cost-minimisation calculation conducted over a two-year time horizon, based on published prices

Parameter	Cost (submission)	Cost (evaluation)	Source/calculation
Ranibizumab intravitreal injection			
Drug costs	$20,999	$11,766	Submission = $1,042.95 per injection (DPMQ) × 10.07 injections per year × 2 years Evaluation = $932.40 per injection (AEMP) × 6.31 injections per year[b] × 2 years
Administration costs	$6,301	$3,949	Submission [evaluation] = $312.95 per administration (MBS item 42738/42739/42740) × 10.07 [6.31] injections per year × 2 years
Total costs	**$27,301**	**$15,716**	Sum of drug and administration costs
Ranibizumab PDS			
Implant cost	$400	$400	Submission stated this was 'As per the PLAC submission'; ocular implant benefit (one-off cost).
Drug cost	$13,920	$11,766	Submission = $3,212.32[a] per dose (proposed DPMQ) × 2.167 administrations per year × 2 years Evaluation = $2,715.44[b] per dose (revised AEMP) × 2.167 administrations per year × 2 years
Administration cost	$2,236	$2,236	$1,558 in Year 1: $1,193.18 for implantation and initial fill (proposed MBS item) + $312.95 per refill exchange (proposed MBS item) × 1.167 (administration frequency of 2.167 minus the initial fill). $678 in Year 2: $312.95 per refill exchange (proposed MBS item) × 2.167 administrations per year.
Monitoring cost	$318	$318	$45.40 per visit (MBS item 105) × 5 visits in Year 1 (Days 1 and 7, Month 1, prior to the first 6 month refill, and then every 3 months in between refills), and 2 visits in Year 2 (every 3 months in between refills).
Supplemental intravitreal ranibizumab	$277	$255	Submission [evaluation] = ($1,042.95 (intravitreal ranibizumab DPMQ) [$932.40 (intravitreal ranibizumab AEMP)] + $312.95 (MBS administration cost items) per injection) × 0.1 supplemental treatments per patient per year (based on 38 supplemental treatments administered over 77.9 weeks in the ARCHWAY trial) × 2 years
Adverse event costs	$79	$79	Based on frequency of adverse events in the ARCHWAY trial multiplied by the costs of treating adverse events.
Explantation costs	$15	$15	= $400 per explantation (proposed MBS item: $400) × 0.019 explantations per year (based on 7 explantations over 77.9 weeks in the ARCHWAY trial) × 2 years
Total costs	**$17,246**	**$15,070**	Sum of implant, drug, administration, monitoring, supplemental intravitreal ranibizumab, adverse event and explanation costs.
Incremental costs	**-$10,055**	**-$646**	=difference between the total costs of ranibizumab PDS and intravitreal ranibizumab

DPMQ = dispensed price for maximum quantity; PDS = port delivery system.
Source: 'Cost minimisation analysis' spreadsheet and Table 3.7, p.96 of the submission.
[a] The proposed published DPMQ of $3,212.32 for ranibizumab PDS corresponds to an ex-manufacturer price of $3,051.10, which was derived using 7.09 injections of intravitreal ranibizumab annually (Table 9).
[b] The evaluation considered that patients may receive 6.31 injections of intravitreal ranibizumab annually in line with the updated DUSC Secretariat analysis, and that this figure should be used across both the calculation for the proposed price for ranibizumab PDS (Table 9) and the cost analysis (Table 10).

6.48 The submission estimated that the ranibizumab PDS would be cost saving over a two-year time horizon ($17,246 compared with $27,301 for intravitreal ranibizumab). The ESC considered it is likely that the net cost savings attributed to ranibizumab PDS compared with intravitreal anti-VEGF have been substantially overestimated, due to the following issues:

- The analysis is highly dependent upon the use and frequency of intravitreal anti-VEGF medicines in practice. This may not have been accurately estimated and is likely to vary, particularly if the proportion of patients maintained on T&E regimens has increased in recent years. This is reflected in the results of the updated DUSC Secretariat analysis, indicating that the average number of intravitreal aflibercept and ranibizumab injections in the second year of treatment has decreased from 7.09 (for patients initiating treatment in 2015) to 6.31 (for patients initiating treatment in 2018). The submission's estimate (10.07 injections per year) would overestimate the number of injections replaced as it included 50% of patients on Q4W injections, who are already accounted for in the DUSC analysis, which comprises all patients including those on Q4W injections and on a T&E regimen. The cost savings are significantly reduced when the cost of intravitreal ranibizumab (for both the price calculation and the cost minimisation calculation) is based on 6.31 injections per year. The PBAC agreed with the ESC that the submission did not adequately justify the proportion of patients on Q4W or T&E regimens expected to transition to ranibizumab PDS, or the median number of intravitreal injections they would have been receiving and considered that the PBS-based contemporary estimate of 6.31 injections per year was a more reliable estimate.
- Additional costs, in particular the cost of adverse events associated with the implant, may have been underestimated, as a number of serious adverse events and adverse events of special interest observed in the trial, which may require surgical or medical intervention, were not included in the economic analysis.
- The extent of use of supplemental intravitreal ranibizumab in practice may differ from that observed in the trial. The PBAC agreed with the ESC that there was a small population (likely ~5%) that requires ongoing supplementary intravitreal ranibizumab. It is possible that these patients would be managed by shortening the time interval between refills, rather than using supplemental intravitreal therapy.
- The appropriate number of monitoring visits is yet to be determined. In the ARCHWAY trial, patients in both treatment arms attended monthly appointments, so the PDS treatment arm aligned with the visit schedule of the monthly ranibizumab comparator arm in order to maintain visual acuity examiner masking and reduce the risk of ascertainment bias. The frequency of monitoring required in clinical practice to address potential adverse events as early as possible is yet to be determined, and the ESC noted that monitoring costs may be increased for ranibizumab PDS in the initial stages of treatment. The PBAC noted that, if the frequency of monitoring visits in patients receiving ranibizumab PDS was not significantly reduced compared to those receiving intravitreal ranibizumab, then some of the perceived patient preference for PDS would no longer be present.

6.49 The PSCR provided additional cost scenarios around replaced intravitreal ranibizumab.

The PSCR acknowledged the uncertainty in dose relativity due to the uncertain average number of additional intravitreal VEGF inhibitor injections required for patients who would switch to ranibizumab PDS but maintained that, in all of the scenarios at published prices, ranibizumab PDS was largely cost neutral or associated with net cost savings. The response updated the submission's base case number of intravitreal ranibizumab injections per year from 10.07 injections to 9.68 injections informed by the updated DUSC Secretariat analysis (50% of patients with 4-weekly injections; 50% on treat and extend regimens receiving 6.31 injections per year). However, the PSCR did not update the price estimate of ranibizumab PDS in this analysis, and stated the sponsor's concerns about [redacted]. Following the ESC Advice, the pre-PBAC response accepted the effective price determination for ranibizumab PDS to be underpinned by 2.17 doses of ranibizumab PDS equivalent to 6.31 injections of intravitreal ranibizumab annually, although the sponsor reiterated [redacted].

6.50 The PBAC noted that this cost-minimisation approach was unable to use the confidential effective price of intravitreal ranibizumab, and therefore it favoured ranibizumab PDS. The PBAC also confirmed that a guiding principle in the cost-minimisation approach is that the Australian Government should not bear the financial risk of any uncertainty because the Australian population already has access to therapy that is at least as effective and safe. Thus, the PBAC considered that inputs to the cost-minimisation calculation should favour the government when uncertain.

Drug cost/patient/year

6.51 The submission estimated that the published drug cost per patient per year for ranibizumab PDS is $6,960 (=2.167 administrations per year × DPMQ $3,212.32); compared with $10,500 per patient per year for intravitreal ranibizumab (=10.07 administrations per year × DPMQ $1,042.95). Based on the updated DUSC Secretariat analysis, the published drug cost per patient per year for ranibizumab PDS is $6,233 (=2.167 administrations per year × DPMQ $2,876.66); compared with $6,581 per patient per year for intravitreal ranibizumab (=6.31 administrations per year × DPMQ $1,042.95). The economic evaluation and financial implications used a consistent approach to estimating drug costs, assuming full compliance.

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC.

6.53 The financial implications presented by the submission were based on published prices. Key inputs are summarised in Table 11.

Table 11: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Value applied and source	Comment
Proportion of AMD that is nAMD	87%; DUSC report into the utilisation of ranibizumab and aflibercept showed that 87% of AMD is nAMD (Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO: Drug Utilisation Sub-Committee (DUSC), May 2018).	This estimate could not be identified during the evaluation. The 2018 DUSC report states that 10-15% of AMD is wet (neovascular) AMD, however the current PBS listings are for nAMD; the treatment of dry AMD with anti-VEGF inhibitors is not recommended. Therefore, it may have been appropriate to assume 100% of scripts were for nAMD.
Patient numbers (derived using average number of scripts per person)	7.09 scripts per year; DUSC report into the utilisation of ranibizumab 10 mg/mL and aflibercept showed that a patient has on average 7.09 injections per year. The total number of scripts was divided by 7.09 to obtain the equivalent number of patients.	This value was based on patients initiating treatment in 2015. The recent shift in treatment algorithms towards treat and extend regimes may have reduced this number in more recent years, as indicated by the updated DUSC Secretariat analysis which estimated 6.31 scripts per year for patients initiating treatment in 2018.
Script equivalence/ substitution rate	0.22 (2.17 prescriptions per year for ranibizumab 100 mg/mL/ 10.07 scripts per year for existing standard of care). Based on the equi-effective doses described in the economic evaluation. Assumes that 50% of the treated population will have the highest treatment burden (monthly; 13.04 injections per year) and 50% will prefer the port delivery system and be on an average number of injections per year (DUSC estimate; 7.09 injections).	The DUSC estimate includes all currently treated patients, representing a distribution of dose numbers. Although patients with the highest treatment burden may be more likely to prefer treatment with the port delivery system, the proportion is an assumption which was not justified. Script substitutions in practice are likely to vary substantially.

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DMO = diabetic macular oedema; DUSC = Drug Utilisation Sub-Committee; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.
Source: Table 4.2, p.102; Table 4.3, p.103-104 of the submission

6.54 The estimated utilisation and financial impact of listing ranibizumab PDS are summarised in Table 12.

Table 12: Estimated use and financial implications (published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submission analysis: using 7.09 scripts per patient for intravitreal ranibizumab and a published DPMQ of $3,212.32 for ranibizumab PDS						
Estimated use and financial implications of ranibizumab PDS						
Projected number of scripts using intravitreal therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients using intravitreal therapies (scripts/7.09)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of ranibizumab implant	5%	10%	15%	15%	15%	15%
Patients electing treatment with ranibizumab implant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total ranibizumab 100 mg/mL scripts (patients × 2.2143)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments ($12.92/script) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS (less copayment) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated changes in use and financial implications of intravitreal therapies						
Changes in script numbers						
- ranibizumab intravitreal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- aflibercept intravitreal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total displaced scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Offsets to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient copayments ($12.92 per script) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Offsets to PBS/RPBS (less copayment) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications to the PBS/RPBS (cost of ranibizumab implant minus cost offsets)						
Net cost to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications to the Government, including MBS costs						
Cost to MBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Offsets to MBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall net cost to Government ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative analysis conducted during the evaluation: substituting 6.31 scripts per patient for intravitreal ranibizumab (updated DUSC Secretariat analysis) and a published DPMQ of $2,876.66 for ranibizumab PDS						
Estimated use and financial implications of ranibizumab PDS						
Projected number of scripts using intravitreal therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients using intravitreal therapies (scripts/6.31)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of ranibizumab implant	5%	10%	15%	15%	15%	15%
Patients electing treatment with ranibizumab implant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total ranibizumab 100 mg/mL scripts (patients × 2.2143)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Copayments ($12.92/script) ($)	[6]	[6]	[6]	[6]	[6]	[6]
Cost to PBS/RPBS (less copayment) ($)	[5]	[13]	[15]	[15]	[22]	[22]
Estimated changes in use and financial implications of intravitreal therapies						
Changes in script numbers						
- ranibizumab intravitreal	[4]	[7]	[12]	[8]	[8]	[8]
- aflibercept intravitreal	[7]	[12]	[14]	[14]	[23]	[23]
Total displaced scripts	[12]	[14]	[11]	[21]	[21]	[21]
Offsets to PBS/RPBS ($)	[5]	[13]	[15]	[22]	[redacted]	[25]
Patient copayments ($12.92 per script) ($)	[6]	[6]	[6]	[6]	[6]	[6]
Offsets to PBS/RPBS (less copayment) ($)	[5]	[13]	[15]	[22]	[22]	[25]
Net financial implications to the PBS/RPBS (cost of ranibizumab implant minus cost offsets)						
Net cost to PBS/RPBS ($)	[6]	[6]	[6]	[6]	[6]	[6]
Net financial implications to the Government, including MBS costs						
Cost to MBS ($)	[6]	[6]	[10]	[6]	[6]	[6]
Offsets to MBS ($)	[6]	[10]	[10]	[5]	[5]	[5]
Net cost to MBS ($)	[6]	[6]	[6]	[10]	[10]	[10]
Overall net cost to Government ($)	[6]	[6]	[10]	[10]	[10]	[10]

Source: Table 4.4, p.105; Table 4.5, p.105; Table 4.6, p.105; Table 4.7, p.106; Table 4.8, p.106; Table 4.9, p.106; Table 4.11, p.107; Table 4.12, p.108; Table 4.14, p.109; Table 4.15, p.110 of the submission; Section 4 workbook

[a] Application of the rounded script substitution rate of 0.22 to 10.07 intravitreal scripts resulted in 2.2143 scripts of ranibizumab 100 mg/mL per patient per year rather than 2.17 (=52/24 weeks).

The redacted values correspond to the following ranges:

[1] 400,000 to < 500,000
[2] 60,000 to < 70,000
[3] 500 to < 5,000
[4] 5,000 to < 10,000
[5] $20 million to < $30 million
[6] $0 to < $10 million
[7] 10,000 to < 20,000
[8] 30,000 to < 40,000
[9] $30 million to < $40 million
[10] $10 million to < $20 million
[11] 70,000 to < 80,000
[12] 20,000 to < 30,000
[13] $40 million to < $50 million
[14] 40,000 to < 50,000
[15] $70 million to < $80 million
[16] $60 million to < $70 million [17]
[17] 500,000 to < 600,000
[18] 100,000 to < 200,000
[19] $100 million to < $200 million
[20] $50 million to < $60 million
[21] 80,000 to < 90,000
[22] $80 million to < $90 million
[23] 50,000 to < 60,000
[24] 90,000 to < 100,000
[25] $90 million to < $100 million

6.55 Based on published prices, the submission estimated savings to the PBS/RPBS of $10 million to < $20 million in Year 1, increasing to $40 million to < $50 million in Year 6, a cumulative total net saving of $200 million to < $300 million over the first six years

of listing. This saving was predominantly driven by a reduction in the corresponding number of scripts for intravitreal anti-VEGF treatments and associated administration costs. The submission assumed that intravitreal ranibizumab and aflibercept patients receive 10.07 scripts annually; however, the updated DUSC Secretariat analysis of ranibizumab and aflibercept utilisation showed the number of intravitreal aflibercept and ranibizumab injections in the second year of use to be 6.31. It is likely that the net cost savings attributed to ranibizumab PDS compared with intravitreal anti-VEGF have been substantially overestimated.

6.56 An analysis conducted during the evaluation, using a revised DPMQ for ranibizumab PDS ($; based on the published AEMP of $2,715.44 derived in Table 9 above) and assuming patient numbers and a script substitution rate based on the updated DUSC Secretariat analysis (6.31 anti-VEGF scripts per year), estimated savings to the PBS/RPBS of $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a cumulative total saving of $20 million to < $30 million over the first six years of listing.

6.57 When MBS costs associated with implantation, administration, monitoring and explantation for ranibizumab PDS and MBS cost offsets associated with reduced administration of substituted intravitreal ranibizumab and aflibercept were included, the submission estimated net savings to the health budget of $10 million to < $20 million in Year 1, increasing to $60 million to < $70 million in Year 6, a cumulative total of $200 million to < $300 million over the first six years of listing, based on published prices. MBS costs associated with adverse events that were included in the cost-analysis were not included in the financial estimates. In a revised analysis conducted during the evaluation, using a DPMQ for ranibizumab PDS of $ (based on the AEMP of $2,715.44 derived in Table 9 above) and assuming patient numbers and a script substitution rate based on the updated DUSC Secretariat analysis (6.31 anti-VEGF scripts per year), estimated net cost savings after MBS cost offsets ranged from $0 to < $10 million in Year 1, increasing to $10 million to < $20 million in Year 6, a cumulative total of $70 million to < $80 million over the first six years of listing. As with the economic evaluation, the ESC considered that monitoring costs may have been underestimated.

6.58 The ESC noted that supplemental intravitreal ranibizumab costs appear not to have been included in the financial estimates.

6.59 The variables with the biggest impact on the financial estimates included the number of equi-effective doses and the uptake rates, which are associated with significant uncertainty. Although a patient receiving more intravitreal anti-VEGF injections per year may be more likely to want to switch to ranibizumab PDS than a patient receiving fewer intravitreal injections per year, the number of scripts likely to be replaced in practice remains highly uncertain. The ESC considered that the 15% uptake appeared poorly justified. At the same time, the ESC considered there was also a small potential for market growth as patients may re-engage with intravitreal treatment in order to access a lower treatment burden PDS.

6.60 The PBAC noted that these financial analyses were unable to use the confidential effective price of intravitreal ranibizumab, and therefore favoured ranibizumab PDS.

Quality Use of Medicines

6.61 No quality use of medicines issues were raised in the submission, and no activities to support the quality use of medicines were proposed. For any new procedure, including the procedure required to implant the device, there may be a higher rate of surgical complications initially as surgeons gain experience. In most cases, complications and adverse events in the ARCHWAY trial were linked to the surgical technique for the port delivery system implant insertion procedure. Some of these risks can be minimised with technique. In addition, clinician and patient education around postoperative care and best practices for activity risk management (e.g., use of protective eyewear), and evaluation of conjunctival status at baseline should also be considered. The port delivery system is a novel drug and device combination that requires a surgical procedure for insertion. Training and education is likely to be important to improve patient outcomes.

6.62 The PSCR provided further information on the peer-to-peer training on implant technique and the simulation training that will be provided to ophthalmologists.

Financial Management – Risk Sharing Arrangements

6.63 A risk sharing arrangement (RSA) was not proposed in the submission. An RSA is in place for anti-VEGF therapies for CNV due to AMD (para 7.14, brolucizumab, PSD, March 2021).

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

7 PBAC outcome

7.1 The PBAC deferred making a recommendation to list ranibizumab delivered via port delivery system (ranibizumab PDS), for the treatment of neovascular age-related macular degeneration (nAMD) in patients who have previously demonstrated a response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment. The PBAC deferred its decision pending availability of the TGA Delegate's Overview, as well as MSAC consideration of the procedures associated with the implanted PDS. The PBAC was of a mind to recommend the PBS listing, noting that the claim of noninferior effectiveness compared with intravitreal ranibizumab was likely reasonable over the longer term. However, it considered that the TGA Delegate's opinion would be informative with respect to the comparative safety claim. The PBAC agreed with the submission that this new formulation would fulfil a clinical need in a subset of nAMD patients, although the size of this subset and the extent of uptake was highly uncertain. The PBAC identified adjustments needed to the submission's base case cost-minimisation approach, including the accepted need to revise the equi-effective doses to take into account the updated analysis by the DUSC Secretariat. The PBAC considered that the net savings to Government in the submission were

overestimated but accepted that there were some cost offsets. Given that the anti-VEFG therapies on the PBS are managed via a Risk Sharing Arrangement, it would be appropriate to apply such arrangements to this new formulation were it listed as well.

7.2 The PBAC acknowledged that there was a clinical place in therapy for ranibizumab PDS, particularly for patients who are unable to extend the intervals of anti-VEGF injections, those who require treatment in both eyes but cannot receive same-day intravitreal injections, and patients in aged care facilities or those otherwise at risk of missing appointments. The PBAC noted the consumer comments from the Macular Disease Foundation Australia (MDFA); the MDFA commented that although ranibizumab PDS will not be appropriate for all patients due to the surgical procedure and associated monitoring, it was supportive of listing ranibizumab PDS to meet the needs of the patient groups mentioned above.

7.3 The PBAC accepted the nominated comparator of intravitreal ranibizumab as a different formulation of the same active ingredient as ranibizumab PDS. The PBAC agreed with the submission that intravitreal ranibizumab could be considered representative of either intravitreal ranibizumab or aflibercept for the clinical and economic comparisons, as the PBAC has previously accepted noninferiority between the two agents and they are priced on an injection:injection basis.

7.4 In terms of the restriction, the PBAC considered that it may be clinically appropriate to require a patient accessing ranibizumab PDS to have been stabilised with prior intravitreal therapy, comprising aflibercept and/or ranibizumab, for a period of at least 6 months, including at least 1 intravitreal ranibizumab injection. The PBAC considered that the clinical evidence more strongly supported use following stabilisation after ranibizumab than after aflibercept, but the PBAC also noted that it would finalise its views on the restriction when making a decision on the PBS listing of ranibizumab PDS.

7.5 The PBAC noted that the submission was based on one head-to-head randomised noninferiority trial, ARCHWAY, which compared treatment with ranibizumab PDS to treatment with intravitreal ranibizumab administered once every four weeks (Q4W), in patients who had previously responded to intravitreal anti-VEGF therapy. Data to Week 36-40 was provided in the submission, and to Week 96 in the PSCR. A long-term extension study, PORTAL, is not due for completion until 2026. The PBAC noted that the Q4W dosing of intravitreal ranibizumab in ARCHWAY did not allow treat-and-extend (T&E) dosing as would be seen in practice (discussed in paragraph 6.38), but this was not a major concern given the noninferiority of such dosing regimens for these drugs. The PBAC also noted the applicability issues raised in terms of the number and types of prior anti-VEGF therapy used in the ARCHWAY trial (in paragraph 6.38), but considered that these issues would be minimised if patients were required to be stabilised on prior anti-VEGF therapy for at least 6 months.

7.6 The PBAC considered that the clinical claim of noninferior effectiveness of ranibizumab PDS compared with intravitreal ranibizumab may be reasonable based

on change from baseline in BCVA score, although there was an initial worsening in BVCA associated with the surgical procedure and a small proportion of patients treated with ranibizumab PDS required supplementary treatment with intravitreal ranibizumab in addition to the 24-weekly refill-exchange procedures. The additional data to Week 96 supplied with the PSCR provided further confidence in the noninferiority conclusion, although ultimately the long-term evidence would only be available with the PORTAL extension study.

7.7 The PBAC considered that the majority of the safety concerns associated with ranibizumab PDS were associated with the surgical procedure to implant the ocular device. The PBAC noted that the safety issues are being considered by the TGA, and it considered that a positive Delegate's Overview would be required to clarify the overall safety profile of the drug.

7.8 The PBAC noted that the submission's base case economic evaluation had made inconsistent assumptions regarding the equi-effective doses in the price calculation and the cost-minimisation calculation (outlined in paragraph 6.43). The pre-PBAC response accepted equi-effective doses for the price calculation in line with the commentary's suggested approach (2.17 doses of ranibizumab being equivalent to 6.31 injections of intravitreal ranibizumab). The PBAC considered that the commentary's revisions in terms of equi-effective doses were potentially conservative, but likely more accurate than the submission's base case, and therefore appropriate in the context of a cost-minimisation approach. The PBAC also noted that the cost-minimisation approach should use ex-manufacturer prices as in the commentary's revisions. The PBAC supported using the effective price of intravitreal ranibizumab and a 2-year time horizon for the cost-minimisation calculation. In addition, the PBAC agreed with the ESC that the net savings estimated were likely overestimated as outlined in paragraph 6.49, and that the monitoring costs associated with ranibizumab PDS should be increased, especially in the first 6 months after the initial dose. The PBAC also suggested that relying on the proposed MBS fees for the implant and explant procedures underestimated the extent of out-of-pocket charges beyond these fees.

7.9 In terms of the estimated budget impact, the PBAC considered that the net savings associated with the potential PBS listing of ranibizumab PDS were likely overestimated in the submission due to overestimating the number of scripts of intravitreal ranibizumab per year. There was also high uncertainty regarding the uptake rate. The PBAC noted that the size of the nAMD market was miscalculated (based on an assumption that only 87% of AMD scripts are for nAMD, when it should be 100%). The PBAC also noted that the budget impact would need to be revised to align with inputs used in the cost-minimisation approach, including increased monitoring costs. The PBAC further noted that the supplementary intravitreal ranibizumab costs were not included in the financial estimates, although it acknowledged that any estimates would be highly uncertain. Based on the information before it, the PBAC accepted that there would be some cost offsets to the Australian Government with the listing of

ranibizumab PDS that would accumulate over time. Nonetheless, given the uncertainty of the estimates and that the anti-VEFG therapies on the PBS are managed via a Risk Sharing Arrangement, it would be appropriate to apply such arrangements to this new formulation were it listed as well.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2022 PBAC PSD

4.02 RANIBIZUMAB, Solution for ocular implant 39.5 mg in 0.395 mL, Susvimo®, Roche Products Pty Ltd.

10 Purpose

10.1 To reconsider ranibizumab delivered via port delivery system (PDS), for the treatment of neovascular age-related macular degeneration (nAMD) in patients who have previously demonstrated a response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment. In March 2022, the PBAC deferred making a recommendation to list ranibizumab PDS, pending availability of the TGA Delegate's Overview, as well as MSAC consideration of the procedures associated with the implanted PDS.

11 Background

11.1 In late 2022, the sponsor paused regulatory activities in Australia whilst undertaking a voluntary recall of the ocular implant in the United States following test results showing that some implants did not perform to standards. The sponsor has advised it is currently pursuing TGA registration (with an updated PDS).

11.2 In March/ April 2022, MSAC deferred its decision regarding the creation of Medicare Benefits Schedule (MBS) items for the PDS to deliver ranibizumab.

11.3 Since PBAC consideration in March 2022, a new anti-VEGF treatment (faricimab) and new presentations of aflibercept have been PBS listed, both of which allow extended treatment intervals (up to 16 to 20 weeks). These listings may be relevant for any future PBAC consideration of ranibizumab PDS.

12 PBAC Outcome

12.1 The PBAC did not recommend the listing of ranibizumab delivered via port delivery system (PDS), for the treatment of neovascular age-related macular degeneration (nAMD) in patients who have previously demonstrated a response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment.

12.2 Noting the previous recommendation (deferral, see paragraph 10.1) was made over 4 years ago and the pending TGA registration of an updated PDS (see paragraph 11.1), the PBAC considered a resubmission would be an appropriate pathway forward for ranibizumab PDS.

12.3 The PBAC noted the MSAC Secretariat had advised a streamlined codependent pathway would be appropriate for a resubmission to MSAC for reconsideration of the procedures associated with the implanted PDS.

12.4 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

13 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.

14 Sponsor's Comment

Roche notes the PBAC's recognition of a clinical place in therapy for ranibizumab PDS (now named Contivue® (ocular implant) and Susvimo® (ranibizumab 100mg/mL). Roche remains committed to bringing this treatment to Australian patients and will re-submit to PBAC in due course.