Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To assess the utilisation of PBS listed medicines for age related macular degeneration (AMD), diabetic macular oedema (DMO), branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

Listing on the Pharmaceutical Benefits Scheme (PBS)

	Abridged restriction	Date listed
Ranibizumab	Subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD).	1 August 2007
Aflibercept	CNV due to AMD.	1 December 2012
Ranibizumab	Visual impairment due to macular oedema (MO) secondary to branch retinal vein occlusion (BVRO) and central retinal vein occlusion (CRVO).	1 July 2015
Ranibizumab	Visual impairment due to diabetic macular oedema (DMO).	1 July 2015
Aflibercept	Visual impairment due to DMO.	1 October 2015
Aflibercept	Visual impairment due to macular oedema secondary to CRVO.	1 October 2015
Aflibercept	Visual impairment due to macular oedema secondary to BRVO.	1 December 2016
Dexamethasone implant	Visual impairment due to DMO for patients unsuitable for, contraindicated to, or who have failed VEGF inhibitors.	1 November 2016

Data Source / Methodology

Data were extracted from the Department of Human Services (DHS) Medicare Pharmacy Claims database for the period August 2007 to December 2017, inclusive.

Key Findings

- The overall use of ranibizumab and aflibercept increased following the listings of DMO and RVO, but the majority of use of ranibizumab and aflibercept is for AMD.
- Use of medicines for AMD continues to grow because of the ageing population and high rates of treatment continuation. In 2017 50,964 patients were treated for AMD. The mean age of patients initiating ranibizumab or aflibercept for AMD was 79 years.
- In 2017, 11,137 patients were treated for DMO with VEGF inhibitors. Use of medicines for DMO has been lower than expected because the number of treated patients and the

number of injections per patient were overestimated. The mean age of patients initiating ranibizumab or aflibercept for DMO was 64 years.

- In 2017, 995 patients were supplied 2,197 dexamethasone implants for DMO. Dexamethasone implant is restricted to use in patients who are unsuitable for, contraindicated to, or who have failed VEGF inhibitors. About half of patients supplied dexamethasone in 2017 had previously received ranibizumab and/or aflibercept.
- In 2017, 10,781 patients were treated for RVO. Use of medicines for RVO is higher than expected because the number of treated patients and continuation rates were underestimated. The average number of injections per patient however has been lower than expected. The mean age of patients initiating ranibizumab or aflibercept for RVO was 73 years. Continuation rates and the number of injections per person are similar for BRVO and CRVO.
- A high proportion (39%) of patients commencing PBS subsidised treatment for RVO had previous or subsequent PBS prescriptions for AMD and/or DMO. This was not anticipated. It is possible that there may have been some use of ranibizumab or aflibercept for RVO outside of the restrictions before it was listed.
- The number of injections per patient is similar whether aflibercept or ranibizumab is used for AMD, DMO or RVO, consistent with the PBAC's consideration that these medicines should be priced on an injection: injection basis.
- Consistent with the disease aetiology, the proportion of bilateral treatment is higher for DMO than for AMD, and very low in RVO. For DMO approximately 30% of prescriptions are supplied with a quantity of two indicating bilateral treatment. For AMD approximately 10% of prescriptions are supplied with a quantity of two.

Contents

Purpose of analysis

To assess the utilisation of PBS listed medicines for age related macular degeneration (AMD), diabetic macular oedema (DMO), branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

Background

Clinical situation

Vision can be affected by the development of abnormal blood vessels within the retina of the eye. The retina is a thin layer of tissue at the back of the eye which receives light that has been focussed on its surface by the lens of the eye. The purpose of the retina is to convert the light it receives into neural signals to the brain for visual recognition. The central portion of the retina, known as the macula, is responsible for focusing central vision in the eye so that objects can be seen in fine detail.

The medicines examined in this review are used for the treatment of the following eye disorders which are caused by abnormal vasculature in the retina: (1) subfoveal choroidal neovascularisation; (2) macular oedema secondary to retinal vein occlusion (RVO); and (3) diabetic macular oedema (DMO). Each disease is discussed in turn below.

Subfoveal choroidal neovascularisation from age-related macular degeneration

AMD manifests as two forms: non-exudative or atrophic (dry); and exudative or neovascular (wet). Wet AMD is relevant to the drugs included in this review and occurs in around 10-15% of overall AMD cases. In wet AMD, abnormal blood vessels (called choroidal neovascularisation or CNV) grow beneath the retina and macula. The macula normally lies in a flat position. When the new blood vessels bleed and leak fluid, this causes the macula to swell which distorts central vision. CNV lesions are classified based on their location relative to the fovea. The fovea is the central area of the macula and provides the sharpest vision. CNV lesions are described as subfoveal if they are located directly below the fovea.

There are no specific Australian clinical guidelines identified for the treatment of AMD. The standard of therapy to treat subfoveal choroidal neovascularisation is anti-VEGF drugs (Horton and Guly, 2017; NICE 2018), including ranibizumab and aflibercept. Bevacizumab is an anti-VEGF drug which is sometimes used to treat AMD, but its use for this condition is 'off-label' as it is not registered in Australia to treat AMD. The anti-VEGF drugs are administered as an injection into the vitreous of the eye under a local anaesthetic. For further details on the mechanism of action of anti-VEGFs, refer to the 'Pharmacology' section below.

Other less commonly used therapies for wet AMD include laser photocoagulation and photodynamic therapy (Bunting and Guymer, 2012). Laser photocoagulation involves ablating blood vessels with a thermal laser and is used in regions away from the fovea. It is

not suitable to treat lesions in the fovea because it can also damage the retina overlying the treated blood vessels. Photodynamic therapy is used for subfoveal neovascular AMD. A photosensitive drug, verteporfin, is intravenously infused which accumulates in the target blood vessels. A non-thermal, low energy laser is applied to the affected region of the retina. This causes the selective thrombotic closure in the abnormal blood vessels. However the effect of photodynamic therapy is only temporary requiring regular re-treatment (Bunting and Guymer, 2012). Verteporfin is PBS subsidised for CNV due to macular degeneration but it is not included in this review as its use is low (77 prescriptions in 2017).[1]

For wet AMD, adjunctive therapy with corticosteroids to an anti-VEGF is not recommended (NICE 2018). Consideration should be given to: switching anti-VEGF for wet AMD if there are practical reasons for doing so this may have limited clinical benefits; observation without anti-VEGF treatment if the disease appears stable; stopping anti-VEGF treatment if the eye develops severe, progressive loss of visual acuity despite treatment; and stopping anti-VEGF treatment if the eye develops late AMD (wet inactive) with no prospect of functional improvement (NICE 2018).

Macular oedema

The build-up of fluid in the macula, called macular oedema, causes the macula to thicken and swell leading to a distortion in vision. Common causes of macular oedema include diabetes and retinal vein occlusion (RVO).

High blood glucose levels caused by diabetes can cause damage to the blood vessels in the retina, a condition called diabetic retinopathy. The two main mechanisms involved are: (1) an impairment of the ability of small blood vessels to regulate the amount of blood passing through them. An excess in blood volumes results in mechanical injury to the vessels causing the leakage of blood; and (2) excess glucose is metabolised to form biochemicals ("glucose metabolites"). This may promote the growth of abnormal blood vessels by binding to proteins in parts of eye to make them function abnormally. The damaged vessels can lead to a significant amount of bleeding into the eye.

Anti-VEGF drugs are considered to be first-line therapy for DMO (The Royal College of Ophthalmologists, 2015; EURETINA guidelines 2017). Laser therapy was previously the standard of care for DMO prior to the availability of anti-VEGF drugs. However laser treatment is now regarded as more harmful than drug therapy (EURETINA guidelines 2017). The dexamethasone corticosteroid implant is also recommended in clinical guidelines to treat DMO, and may be more appropriate than alternative therapies in patients who have had a recent cardiovascular event or who would prefer to not have monthly injections (The Royal College of Ophthalmologists, 2015).

RVO involves a blockage of the vessel which drains blood out of the retina. This causes increased pressure within the blood vessel resulting in blood and fluid leaking from the vessel into the retina and macula. The build-up of fluid in macula, called macula oedema,

[1] DHS Prescriptions database, data extraction based on the date of supply.

causes the macula to thicken and swell leading to a distortion in vision. Retinal vein occlusions are referred to as central retinal vein occlusion (CRVO) when the blockage is in the main retinal vein. Blockages within the smaller branch veins are classified as branch retinal vein occlusion (BRVO). In the majority of cases, ischaemic CRVO does not improve without treatment (Shah, 2012). BRVO can spontaneously resolve and a patient may be observed to allow for this before initiating therapy (Shah, 2012).

The main treatments for macular oedema due to RVO are the anti-VEGF drugs (Sivaprasad et al., 2015; The Royal College of Ophthalmologists, 2015). Laser photocoagulation has been shown to have a potential role for BRVO but not for CRVO. Treatment with corticosteroids improves visual acuity from RVO-related macular oedema but their use is associated with serious ocular side effects, including secondary glaucoma and the formation of cataracts (Sivaprasad et al., 2015). The PBAC considered an application to list dexamethasone implant on the PBS for RVO at the March 2018 meeting. See 'Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee' section for further information.

Switching between anti-VEGF agents and between dexamethasone and an anti-VEGF agent to treat macular oedema is recommended in guidelines (The Royal College of Ophthalmologists, 2015). However, the longer-term outcomes of combination or sequential treatment of anti-VEGF agents and dexamethasone are unknown (The Royal College of Ophthalmologists, 2015).

Pharmacology

Vascular endothelial growth factor (VEGF) promotes the formation of new blood cells. VEGF also binds to tyrosine kinase receptors on endothelial cells causing vascular leakage.

Aflibercept and ranibizumab bind to VEGF to prevent the interaction of VEGF with its receptors on the surface of endothelial cells. Aflibercept and ranibizumab act to reduce the formation of new blood cells, the proliferation of endothelial cells and vascular leakage.

The World Health Organization Anatomical Therapeutic Chemical (ATC) classification codes for aflibercept and ranibizumab administered into the eye are S01LA05 and S01LA04, respectively.[2]

Dexamethasone is a potent corticosteroid which is implanted in the vitreous of the eye. The implant is made of a biodegradable polymer which gradually disintegrates over several months into carbon dioxide and water as dexamethasone is released (Yonegawa and Wolfe, 2015). The biologic action of corticosteroids includes the down regulation of VEGF. As such, dexamethasone has antiangiogenic (i.e. inhibits the formation of new blood cells) and anti-vascular permeability effects (Yonegawa and Wolfe, 2015).

The ATC code for dexamethasone administered into the eye is S01BA01.[3]

[2] https://www.whocc.no/atc
[3] https://www.whocc.no/atc

Therapeutic Goods Administration (TGA) approved indications

Table 1: TGA approved indications (abridged)

	Ranibizumab	Aflibercept	Dexamethasone Implant
Neovascular (wet) age-related macular degeneration	✓	✓	
Visual impairment due to diabetic macular oedema	✓	✓	✓
Visual impairment due to macular oedema secondary to retinal vein occlusion	✓	✓	✓
Visual impairment due to choroidal neovascularisation	✓		
Visual impairment due to choroidal neovascularisation secondary to pathologic myopia	✓		
Visual impairment due to myopic choroidal neovascularisation		✓	
Non-infectious uveitis affecting the posterior segment of the eye			✓

[a] subfoveal choroidal neovascularisation due to AMD or caused by other macular disease.
Source: Lucentis (ranibizumab) Australian approved product information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 27 February 2007, last updated 30 January 2015.
Eylea (aflibercept) Australian approved product information. Pymble: Bayer Australia Ltd. Approved 7 March 2012, last updated 15 April 2015.

Dosage and administration

The recommended dose and administration for ranibizumab, aflibercept and dexamethasone by their listed indications are summarised in Table 2. For each indication, the current recommended frequency of administration for aflibercept and ranibizumab are the same.

Table 2: Dosage and administration of ranibizumab, aflibercept and dexamethasone implant

Ranibizumab (Lucentis), Novartis Pharmaceuticals Australia Pty Ltd[1]
Dose
Recommended dose is 0.5 mg given as a single intravitreal injection. The maximal dose (0.5 mg) should not be exceeded.
Frequency of administration
The interval between two doses injected into the same eye should be at least four weeks. The frequency of administration varies by indication.
Neovascular (wet) age-related macular degeneration[2]
Initiated with one injection per month for three consecutive months, followed by one injection every two months. The dosing interval can be extended up to every three months when optimal visual acuity is achieved.
Central retinal vein occlusion and branch retinal vein occlusion
Initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Diabetic macular oedema
Initiated as one injection per month for five consecutive months, then one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes.
Aflibercept (Eylea), Bayer Australia Ltd[3]
Dose
Recommended dose is 2 mg given as a single intravitreal injection.
Frequency of administration
The interval between two doses injected into the same eye should be not be shorter than one month.
Neovascular (wet) age-related macular degeneration
Initiated with one injection per month for three consecutive months, then one injection every two months. The dosing interval can be extended up to every three months.
Central retinal vein occlusion and branch retinal vein occlusion
Initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.
Diabetic macular oedema
Initiated with one injection per month for five consecutive months, then one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes.
Dexamethasone (Ozurdex), Allergan Australia Pty Limited[4]
Dose
Recommended dose is 700 micrograms per eye. This is the entire contents of the single use Ozdurex device.
Frequency of administration
Administration in both eyes on the same day is not recommended.
Diabetic macular oedema
A six monthly dosing interval was used in in the pivotal clinical trials. In clinical trials, most retreatments were administered between 5 and 7 months after a prior treatment. There is no experience of the efficacy and safety of repeat administrations beyond 7 implants.

Source:

[1] Lucentis (ranibizumab) Australian approved product information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 27 February 2007, last updated 22 August 2017.

[2] At the time of first listing, the Product Information recommended that ranibizumab be given as a monthly injection. Former versions of the Product Information noted that after the first three injections, the frequency of injections could be reduced to one injection every 3 months if monthly injections were not feasible.

[3] Eylea (aflibercept) Australian approved product information. Pymble: Bayer Australia Ltd. Approved 7 March 2012, last updated 13 July 2016.

[4] Ozurdex® (dexamethasone implant), Australian Approved Product Information. Gordon NSW: Allergan Australia Pty Ltd. Approved 4 June 2015, updated 6 June 2017.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at 1 February 2018)

Table 3: PBS listing of ranibizumab

Item	Name, form & strength, pack size	Indications	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
1382R	ranibizumab 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	AMD BRVO CRVO	1	2	$1149.44*	Lucentis Novartis Pharmaceuticals Australia Pty Limited
10138N	ranibizumab 1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe	AMD BRVO CRVO	1	2	$1149.44*	
10374B	ranibizumab 1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe	DMO	1	5	$1149.44*	
10373Y	ranibizumab 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	DMO	1	5	$1149.44*	

*special pricing arrangement applies
Source: http://www.pbs.gov.au/medicine/item/10138N-1382R

Table 4: PBS listing of aflibercept

Item	Name, form & strength, pack size	Indications	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
2168D	aflibercept 4 mg/0.1 mL injection, 1 x 0.1 mL vial	AMD BRVO CRVO	1	2	$1149.44*	Eylea Bayer Australia Ltd
10505X	aflibercept 4 mg/0.1 mL injection, 0.1 mL vial	DMO	1	5	$1149.44*	

*special pricing arrangement applies
Source: http://www.pbs.gov.au/medicine/item/2168D

Table 5: PBS listing of dexamethasone implant

Item	Name, form & strength, pack size	Indications	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10943Y	dexamethasone 700 microgram implant, 1	DMO	1	1	$1354.79*	Ozurdex Allergan Australia Pty Limited

*special pricing arrangement applies
Source: http://www.pbs.gov.au/medicine/item/10943Y

Restriction

Ranibizumab, aflibercept and dexamethasone are Authority Required listings. For all listed indications for each medicine, the first authority application for each eye must be made in writing or by telephone. For all medicines, Authority applications for continuing treatment in the same eye may be made by telephone. At the time of approval, the patient's indication is recorded in the Authority database. A patient must be treated by an ophthalmologist or in consultation with an ophthalmologist.

Ranibizumab and aflibercept are PBS listed for the treatment of:

- Subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD).
- Branch retinal vein occlusion with macular oedema. Initiating patients must have visual impairment due to macular oedema secondary to BRVO, and must have documented visual impairment defined as a best corrected visual acuity score between 73 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/400), in the eye proposed for treatment.
- Central retinal vein occlusion with macular oedema. Initiating patients must have visual impairment due to macular oedema secondary to CRVO, and must have documented visual impairment defined as a best corrected visual acuity score between 73 and 24 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/320), in the eye proposed for treatment.
- Diabetic macular oedema. Initiating patients must have visual impairment due to diabetic macular oedema, and must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment.

Dexamethasone is listed for diabetic macular oedema. Patients may only access dexamethasone if they are unsuitable for, or contraindicated to, treatment with VEGF inhibitors, or have failed prior treatment with VEGF inhibitors. Initiating patients must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment.

There are no continuation criteria in the PBS restrictions for any of the listed indications for patients to access continuing treatment.

For the diabetic macular oedema listings, the drugs are given either as monotherapy or in combination with laser photocoagulation.

For details of the current PBS listing refer to the PBS website.

To initiate treatment for all PBS listings of aflibercept, dexamethasone and ranibizumab, each eye condition must be diagnosed using either fluorescein angiography or optical

coherence tomography. There is a specific Medicare Benefits Schedule item (Item 11219) to claim for optical coherence tomography (OCT) when this procedure is done to fulfil the requirements of the PBS restrictions. Only one MBS service for OCT can be claimed over a 12 month period. MBS items (Items 11215 and 11218) are also available for retinal angiography. There is also a MBS item for the intravitreal injection of therapeutic substances (Item 42740).

Further information on the MBS items can be obtained from MBS Online.

Date of first listing on PBS

- Ranibizumab listed 1 August 2007
- Aflibercept listed 1 December 2012
- Dexamethasone implant listed 1 November 2016

Changes/additions to listing

Table 6: Changes to PBS listings of medicines for AMD, DMO and RVO

Listing details	PBAC recommendation	Date listed
Ranibizumab first listed for CNV due to AMD as a vial presentation.	March 2007	1 August 2007
Aflibercept first listed for CNV as a vial presentation.	March 2012	1 December 2012
A pre-filled syringe presentation of ranibizumab was listed for CNV due to AMD.	March 2014	1 September 2014
Ranibizumab first listed for visual impairment due to MO secondary to RVO (both BRVO and CRVO).	July 2014	1 July 2015
Ranibizumab first listed for visual impairment due to DMO.	July 2014	1 July 2015
The ranibizumab 2.3 mg/0.23 mL solution for injection and ranibizumab 1.65 mg/0.165 mL pre-filled syringe presentations for ranibizumab were 'a' flagged in the Schedule (to enable pharmacists to substitute the two presentations).	November 2014	1 March 2015
The listing of aflibercept was extended to include treatment of a patient with visual impairment due to DMO.	November 2014	1 October 2015
The listing of aflibercept was extended to include treatment of MO due to CRVO.	November 2014	1 October 2015
The listing of aflibercept was extended to include treatment of a patient with MO secondary to BRVO.	November 2015	1 December 2016
Dexamethasone listed for visual impairment due to DMO.	March 2016	1 November 2016

Note: AMD, aged related macular degeneration; BRVO, branch retinal vein occlusion; CNV, subfoveal choroidal neovascularisation; CRVO, central retinal vein occlusion; DMO, diabetic macular oedema; MO, macular oedema; RVO, retinal vein occlusion.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The main recommendations made by PBAC relevant to the review are summarised below by indication.

Subfoveal choroidal neovascularisation (CNV)

Verteporfin was the first listing for subfoveal choroidal neovascularisation due to age related macular degeneration, recommended by PBAC in November 2005. It was listed on a cost-effectiveness basis against standard care (comprising of no treatment or watchful waiting). The PBAC has subsequently recommended ranibizumab (March 2007) and aflibercept (March 2012) for this indication.

Ranibizumab was listed on a cost-effectiveness basis against verteporfin. The listed presentation of ranibizumab was one vial containing 3.0 mg in 0.3 mL. The PBAC noted that there was a large fill volume of the vial relative to the recommended dose (0.5 mg) where only around one sixth of the vial would be used. The PBAC considered that the pack size would result in a large amount of wastage and asked the sponsor to investigate the provision of a smaller pack size. In March 2009, the PBAC recommended the listing of a lower fill volume of 0.23 mL to replace the 0.3 mL fill volume. This was intended to reduce wastage. The 2.3 mg in 0.23 mL presentation of ranibizumab was listed from April 2009.

Following a recommendation by PBAC in March 2014, a pre-filled syringe presentation containing 1.65 mg of ranibizumab in 0.165 mL was listed from 1 September 2014. Listing was recommended on a cost minimisation basis with the listed vial presentation.

Aflibercept was recommended on a cost-minimisation basis with ranibizumab. The submission had based the cost minimisation analysis on the treatment frequency in the Product Information for aflibercept (7 per year) and current practice based on PBS data for ranibizumab (8.8 per year). The PBAC considered it was uncertain whether less frequent injections would eventuate with aflibercept treatment compared to ranibizumab treatment. The PBAC considered that the price of aflibercept should be based on an injection: injection basis with ranibizumab with one aflibercept 2 mg injection equivalent to one ranibizumab 0.5 mg injection. The PBAC noted the advice from its DUSC that approximately 20 percent of patients were receiving bilateral treatment with ranibizumab. The PBAC considered that the submission's estimate of the number of prescriptions dispensed for aflibercept was likely to be underestimated as it was based on single eye treatment.

The PBAC recommended that an appropriate price and risk-share agreement be negotiated such that the listing of aflibercept would be cost-neutral to the PBS and that both ranibizumab and aflibercept should share the same cap.

For further details refer to the Public Summary Documents from the November 2011, March 2007 and March 2012 meetings.

Diabetic macular oedema

The PBAC recommended ranibizumab in July 2014 as the first listing to treat diabetic macular oedema on a cost-effectiveness basis against laser treatment. The PBAC noted that a set treatment duration was assumed in the financial estimates. However, as the requested restriction did not have a definitive stopping rule, use in practice could be longer than assumed by the submission.

Aflibercept received a recommendation from PBAC in November 2014 to treat diabetic macular oedema on a cost-minimisation basis with ranibizumab. The PBAC recommended the equi-effective doses of aflibercept 2 mg injection and 0.5 mg ranibizumab injection and a 1:1 injection relativity between the drugs. The PBAC considered that the financial estimates presented in the submission were overestimated. This included the assumptions for the population with clinically significant macular oedema who had visual impairment and the prevalence rates for the disease.

The dexamethasone implant was recommended by PBAC in March 2016 on the basis of inferior effectiveness and inferior safety compared to ranibizumab and aflibercept, and thus on appropriately adjusted estimates of cost-effectiveness. The submission requested a PBS listing for patients with the same visual impairment as other DMO listings, with an additional requirement that patients must have a pseudophakic lens in the treatment eye; or be scheduled for cataract surgery. The submission suggested that this population would include those who have a contraindication to or have failed to respond to VEGF inhibitors, or where a patient may be unsuitable for treatment with VEGF inhibitors because of a likelihood of failure to attend the clinic on the number of occasions required. The final PBS restriction included as a clinical criteria that initiating patients must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors, or must be unsuitable for treatment with VEGF inhibitors, or must have failed prior treatment with VEGF inhibitors.

The PBAC noted that there would be no cost offsets for patients unsuitable for VEGF inhibitors. As such, the PBAC considered there would be some growth in the current market rather than assuming substitution for VEGF inhibitors as the basis for claiming overall cost savings. The PBAC noted that the financial estimates were most sensitive to assumptions for the treatment uptake rate.

For further details refer to the Public Summary Documents from the July 2014, November 2014 and March 2016 meetings.

Macular oedema secondary to retinal vein occlusion

Ranibizumab was the first listing for the treatment of visual impairment from macular oedema secondary to RVO (both BRVO and CRVO). The PBAC recommended the listing in July 2014 on the basis of cost-effectiveness over laser treatment. It was noted that there was the potential for use beyond the requested restriction as the interpretation of a response could be higher in clinical practice compared to the clinical trials. In the RESTORE trial, treatment with ranibizumab was suspended if there was no further improvement in the Best-Corrected Visual Acuity (BCVA) letter score at the last two consecutive visits or if a

BCVA score greater than or equal to 84 (Snellen equivalent 20/20) was observed at the last two consecutive visits (Mitchell et al., 2011).

The PBAC recommended the extension of aflibercept's listing to treat macular oedema secondary to CRVO in November 2014 and secondary to BRVO in November 2015. These recommendations were on the basis of cost-minimisation to ranibizumab. For the CRVO submission, the PBAC noted that the estimated costs were sensitive to the estimated number of injections per patient per year. While the TGA Product Information had been revised to reduce the number of monthly injections from six to three in the loading dose phase, the PBAC considered that re-injections after three months remained a source of uncertainty because of a lack of new sources of evidence. For the CRVO and BRVO listings, the PBAC recommended a 1:1 dose relativity to ranibizumab with the equi-effective doses of aflibercept 2 mg injection and 0.5 mg ranibizumab injection.

For further details refer to the Public Summary Documents from the July 2014 and November 2014 and November 2015 meetings.

At the March 2018 meeting, the PBAC recommended extending the listing of dexamethasone implant for patients with RVO who have failed or are contraindicated to VEGF inhibitors. The recommendation was based on clinical need, acceptable clinical effectiveness compared to placebo, and the broader context of the existing listing of dexamethasone for diabetic macular oedema. The clinical trial data for dexamethasone implant compared with placebo showed a modestly improved benefit with dexamethasone implant for some patients (a difference of between 6 to 9 gain in letters in best corrected visual acuity over placebo at 2 months), with the efficacy of the dexamethasone implant waning beyond month 3.

The PBAC did not recommend extending the listing to patients with RVO who are considered 'unsuitable' for VEGF inhibitors, due to the ambiguity of the proposed restriction wording leading to potential use of an inferior and more harmful therapy than a VEGF inhibitor, based primarily on convenience. The clinical need for an alternative therapy for patients who may respond to a VEGF inhibitor but in whom monthly injections may be difficult, was not adequately supported to make available a sub-optimal therapy for a generally short-term condition.

Approach taken to estimate utilisation

The approach taken to estimate utilisation for the AMD submissions to the PBAC are summarised in Appendix A. The approach taken to estimate utilisation for the DMO and RVO submissions to the PBAC are summarised in the 'Analysis of actual versus predicted utilisation' section later in the report.

Previous reviews by the DUSC

A predicted versus actual analysis of ranibizumab considered by DUSC in June 2009 found that the actual numbers of patients receiving ranibizumab were greater than estimated but the number of prescriptions/injections supplied and R/PBS benefits paid during the first year of listing were lower than estimated.

A subsequent analysis of ranibizumab, considered by DUSC in February 2012, found that patterns of treatment did not match to the suggested once monthly treatment recommendation. The average number of prescriptions per patient in their first twelve months of treatment was lower than expected, but was increasing over time. In a cohort commencing in August 2007 each patient had on average 5.84 prescriptions in the first 12 months and a cohort commencing in August 2010 had 7.42 in the first 12 months.

The DUSC noted that with an ageing population and the correlation between age and age related macular degeneration, the prevalence rates are likely to continue to increase and thus the number of patients treated is also likely to increase. The Committee also questioned whether the pattern of treatment varied based on age, and if more aggressive treatment protocols were used in younger patients.

This review was considered by the PBAC at its March 2012 meeting. The PBAC noted that the treated prevalence of CNV-AMD is continuing to increase and patients are being treated for a longer period than expected in the original submission for ranibizumab considered by the PBAC. The number of prescriptions per patient in the first 12-months of therapy is also increasing reflecting clinician's using more frequent administration of ranibizumab over the 4 years since listing. A response to the review provided to DUSC on behalf of retinal specialists reported that clinicians are using a "treat and extend" regimen for management of CNV-AMD which is similar to the protocol in the CATT Trial.

In June 2015 DUSC considered an analysis of the use of ranibizumab, aflibercept and verteporfin for age related macular degeneration (AMD), including a 24 month predicted versus actual analysis of aflibercept.

The review found that the majority of patients remain on treatment for many years and therefore the total number of patients continues to grow. Approximately half of patients are treated for at least 4 years, and there are almost 3,000 patients who are in their seventh year of treatment. The PBAC recommendations were based on clinical trials of one or two year duration, and a modelled economic evaluation for ranibizumab with a 5 year time horizon. The PBS data show an average age of initiation of 80 years. DUSC noted that the average expected age of death of 84-87 years based on ABS statistics would indicate that many patients would not be treated beyond 7 years, but considered that some individuals will likely use aflibercept or ranibizumab for longer periods of time. DUSC considered that discontinuation rates have been lower than anticipated, and duration of use longer than anticipated contributing to the growth in the prevalent number of patients treated. DUSC noted advice from clinicians that there is minimal trial data to guide decisions regarding treatment cessation, but that ongoing treatment reduces disease progression as well as reducing the risk of a sudden recurrence of disease.

The average number of injections per treated patient increased between 2007 and 2010. From 2011 onwards the number of injections per patient appears to have stabilised, with new patients receiving an average of 8.4 injections in their first year of treatment, and continuing patients receiving an average of 7.1 injections per year. DUSC noted that it the patterns of use evolved over several years from the time when ranibizumab was listed and

considered it too early to assess whether the availability of aflibercept will change patterns of use in Australian clinical practice.

The rate of bilateral treatment appears to be increasing, although there is limited information available to estimate this use. DUSC agreed that bilateral use is increasing over time based on the proportion of prescriptions with an increased maximum quantity of injections. However DUSC considered that this measure underestimates bilateral treatment as it only captures simultaneous bilateral use, whereas bilateral use may also include each eye treated consecutively or alternately. DUSC noted that ophthalmologists are required to specify which eye is being treated when seeking an authority approval to prescribe ranibizumab or aflibercept, but that these data are not readily accessible. DUSC agreed with Stakeholder views that in order to assess the true extent of bilateral treatment the dataset would need to include which eye is being treated.

There was rapid uptake of aflibercept following its PBS listing, reaching approximately 50% of the AMD market within 6 months. Aflibercept is used both in new patients and in prevalent patients who switched from ranibizumab. The number of injections of ranibizumab or aflibercept per patient appeared to be similar.

DUSC anticipated that utilisation of aflibercept and ranibizumab for wet AMD will continue to increase into the future due to an ageing population, high rates of continuation on treatment and a high number of injections per patient per year. DUSC agreed that overall utilisation increases into the future are likely for these reasons. In addition, DUSC noted that utilisation is lower in some states and territories and commented there is potential for the number of treated patients and the number of injections per patient per year to increase if capacity increases.

For details of the DUSC consideration of aflibercept and ranibizumab for age-related macular degeneration refer to the Public Release Document from the June 2015 DUSC meeting.

Methods

PBS prescription data for ranibizumab, aflibercept, and dexamethasone implants from 1 August 2007 to 31 December 2017 were extracted from the DHS prescription database based on the date of dispensing. The date of processing of PBS prescriptions may differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from DHS Medicare website[4]).

PBS prescription data were used to determine the number of prescriptions supplied and to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period).

[4] PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

Indication matching

As some PBS item numbers cover multiple indications, the DHS Authority approvals data was used to match claims with indications of AMD, DMO or RVO. Overall, 99.63% of claims were matched with authority codes.

Matched	2,114,702
Not matched	7,757
Total claims since 2007	2,122,459

Of the more than 2 million claim records, there were 12,402 claims belonging to 5,063 patients with blank indications due to no authority number or DVA authority being recorded.

Prescriptions with blank indications were assigned the indication of the majority of the prescriptions for that patient. There were 1,196 claims belonging to 484 patients without any indication on any prescription. These patients are included in overall counts of prescriptions and injections but not in indication specific analyses.

For each patient, the total number of indications they have received treatment for were counted. Patients who have been treated for more than one indication were included in counts of initiating and treated patients for that indication and the predicted versus actual analyses. These patients were excluded from analyses of continuation rates, average number of injections supplied, proportions of prescriptions with increased quantities, and age and geographical location of patients. Information about the number of patients who received treatment for one or more indications is provided in a later section.

Overall Utilisation

The number of patients supplied ranibizumab and/or aflibercept was determined by counting the number of deidentified personal identification numbers (PINs) in the prescription data over the specified time period. Incident patients are identified by their first prescription for either ranibizumab or aflibercept, since the PBS listing of ranibizumab on 1 August 2007. A patient is assumed to remain on treatment if he or she had further prescriptions of either ranibizumab or aflibercept, no matter how much time has elapsed since the last treatment, whether the patient has been authorised for a second eye, or whether the patient has switched medicine.

Grandfathered and incident patients are grouped in the current analysis.

Patient characteristics

The characteristics of age and state of residence, as determined by Medicare enrolment, of patients are reported. These characteristics are identified at the initial prescription. In some analyses patient numbers have been standardised by population to allow comparison across states. The estimated number of patients in the relative year has been used to allow comparison through time and across states.

Number of injections per patient

The number of injections per patient per year was examined using deidentified individual patient data. The cohorts comprised patients who were supplied an initial prescription for the indication being investigated, in each calendar year. Patients' prescription histories were followed for 12 month periods, from the date of their first supplied prescription, to the end of December 2017. The follow-up period varies from one year for those who initiated treatment in 2016, to 10 years for those who initiated in 2007. For patients initiating in 2017 there is insufficient follow-up data to assess the number of injections supplied over a full 12 months. The injections per patient analyses are presented as mean values for each available 12 month period for each cohort.

To compare the patterns of use of aflibercept and ranibizumab, an analysis of the cohort of patients who initiated in 2015 (for AMD with 24 months follow up) and 2016 (for DMO and RVO with 12 months follow up) are further examined by their initiating and subsequent drugs.

Analyses were undertaken in SAS.

Results

Analysis of ranibizumab and aflibercept for AMD

Ranibizumab has now been listed for AMD for more than 10 years. The most recent DUSC reviews found that the majority of patients remain on treatment for many years and the total number of patients on treatment continued to grow. The previous reviews found the average number of injections per treated patient had increased between 2007 and 2010 and was stable from 2011 to 2014.

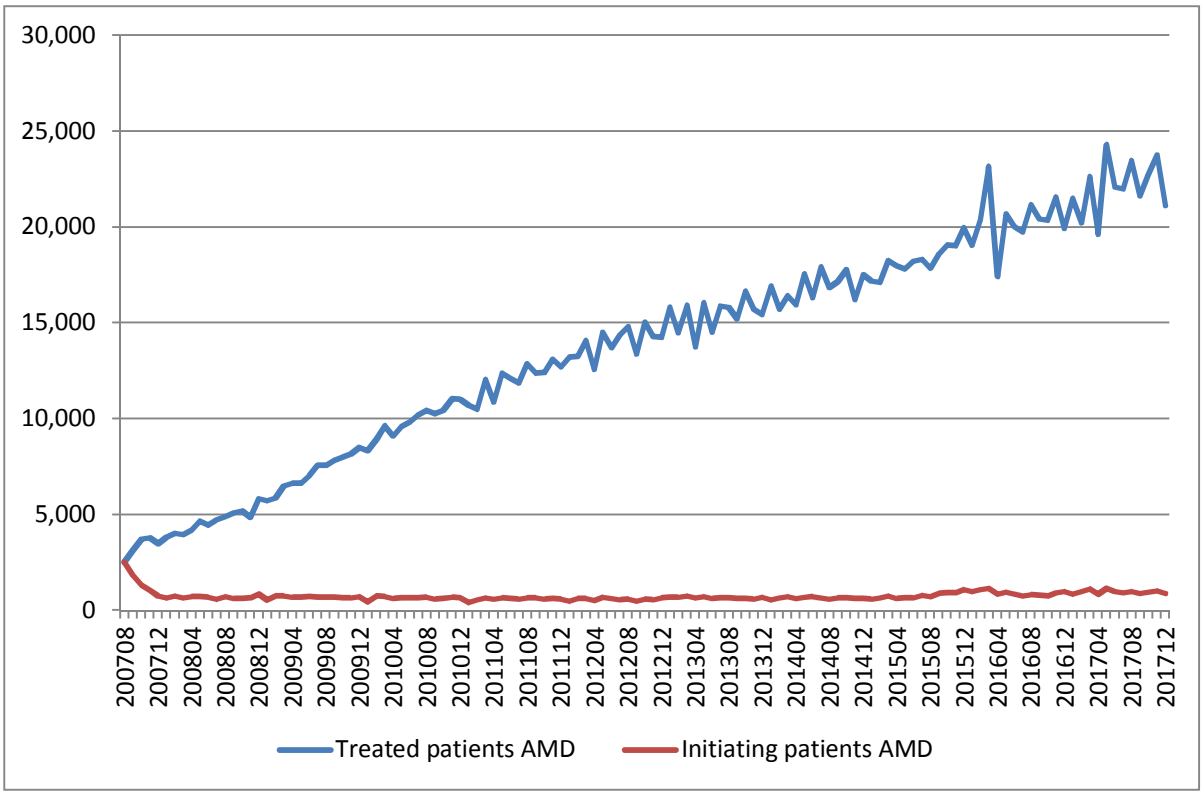

Figure 1: Initiating and prevalent treated patients for AMD

Figure 1 shows the number of AMD patients initiating and treated per month, which includes both aflibercept and ranibizumab. This suggests the number of patients being treated is still growing.

Table 7 below summarises these patients by year and calculates the number of injections per prevalent patient. This suggests the number of injections per patient has stabilised.

The rate of growth of incident patients has been variable and was higher in 2015 and 2016 than in previous years.

Table 7: Summary of patients accessing treatment for AMD and number of supplied prescriptions, supplied injections and injections per patient by calendar year

Year	New patients	Rate of change from previous years new patients	Prevalent patients	Initiating patients per pop ≥65/1000	Treated patients per pop≥65/1 000	Prescriptions supplied	Injections supplied	Calculated injections per prevalent patient
2007	7,457		7,457	3.11	3.11	17,459	18,467	2.48
2008	8,128	9%	14,240	3.31	5.81	59,614	63,002	4.42
2009	8,104	0%	18,863	3.22	7.49	93,045	98,567	5.23
2010	7,625	-6%	22,801	2.95	8.81	130,739	140,163	6.15
2011	7,071	-7%	26,094	2.65	9.76	160,116	172,467	6.61
2012	6,844	-3%	29,234	2.48	10.61	188,042	203,768	6.97
2013	7,737	13%	33,315	2.72	11.71	208,861	227,130	6.82
2014	7,590	-2%	36,712	2.56	12.36	229,504	250,242	6.82
2015	9,105	20%	41,126	2.96	13.35	249,684	273,311	6.65
2016	10,743	18%	46,910	3.37	14.72	281,176	309,370	6.59
2017	11,453	7%	50,964	3.47	15.44	304,952	337,630	6.62

The figure for 2007 represents the first five months of listing
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Injections per patient and continuation rates

The following tables represent the cohorts of patients who initiated in each calendar year. Individual patients were followed in 12 month periods from their initiation date. A patient is assumed to remain on treatment if he or she had further prescriptions of either ranibizumab or aflibercept, no matter how much time has elapsed since the last treatment, whether the patient has been authorised for a second eye, or whether the patient has switched medicine. This means a patient may have experienced disease in one eye in 2007 and initiated treatment, then failed and stopped treatment for months or years, and later experienced disease in their second eye.

The number of patients who initiated in 2017 is known, but there is insufficient data available to assess how many injections they received in their first full twelve months of treatment.

Table 8: Number and percentage of patients remaining on treatment by initiating year

Patient numbers by initiating year and year of treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
2007	7,457	4,853	4,270	3,883	3,578	3,262	2,932	2,641	2,335	2,055	1,566
2008	8,128	5,073	4,299	3,903	3,531	3,220	2,889	2,562	2,282	1,729	
2009	8,104	5,373	4,606	4,153	3,756	3,376	2,975	2,656	2,053		
2010	7,625	5,352	4,628	4,112	3,699	3,285	2,940	2,270			
2011	7,071	5,204	4,542	4,006	3,598	3,178	2,442				
2012	6,844	5,160	4,510	3,996	3,603	2,754					
2013	7,737	5,957	5,199	4,652	3,655						
2014	7,590	5,882	5,121	3,982							
2015	9,105	6,529	4,797								
2016	10,743	6,307									
2017	11,453										

Percentage of continuing patients from the number of initiators in year 1

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
2007	100%	65%	57%	52%	48%	44%	39%	35%	31%	28%	21%
2008	100%	62%	53%	48%	43%	40%	36%	32%	28%	21%	
2009	100%	66%	57%	51%	46%	42%	37%	33%	25%		
2010	100%	70%	61%	54%	49%	43%	39%	30%			
2011	100%	74%	64%	57%	51%	45%	35%				
2012	100%	75%	66%	58%	53%	40%					
2013	100%	77%	67%	60%	47%						
2014	100%	77%	67%	52%							
2015	100%	72%	53%								
2016	100%	59%									

The majority of patients continue into the second year of treatment. Since 2011, over 70% of patients have received treatment in their second year. The exception is patients who initiated in 2016 where only 58.71% of patients received a treatment in 2017. The reason for this is unknown. Continuation rates of earlier cohorts in subsequent years remain high. The continuation rates calculated from the previous year rather than initial year are 65 to 75% from year 1 to year 2, and then around 88 to 90% in subsequent years.

The table below displays the mean number of injections of ranibizumab and aflibercept that patients received in each year of treatment, by the calendar year of initiation.

Patients who have been recorded as being treated for more than one indication (i.e. AMD and DMO or AMD and RVO) are not included in this analysis.

Table 9: Average number of injections supplied in each 12 months of therapy for patients by initiating year

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Initiated 2007[a]	5.72	5.95	7.18	7.67	8.00	7.88	7.67	7.39	7.42	7.63
Initiated 2008	6.15	6.12	6.99	7.38	7.65	7.41	7.32	7.20	7.25	
Initiated 2009	7.26	6.77	7.31	7.50	7.30	7.23	7.38	7.41		
Initiated 2010	8.11	7.20	7.41	7.44	7.46	7.45	7.54			
Initiated 2011	8.35	7.19	7.10	7.27	7.36	7.38				
Initiated 2012	8.52	7.04	7.11	7.30	7.48					
Initiated 2013	8.33	6.85	7.07	7.22						
Initiated 2014	8.46	6.97	7.10							
Initiated 2015	8.53	7.08								
Initiated 2016	8.40									

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

[a] This cohort may also contain some patients who were grandfathered on to ranibizumab and therefore are not initiators to the therapy.

Table 9 show the number of injections supplied in the first 12 months of therapy now appears to be stable at around 8.4 prescriptions per year. In the second year of treatment the average number of injections is generally lower than the first year of treatment. In subsequent years the average increases, possibly because of the interplay between patients who have ceased treatment due to non-response, have stable disease and are being observed, have developed bilateral disease and/or require ongoing monthly treatment to manage their condition.

Number of injections per patient by medicine

Aflibercept was recommended on a cost-minimisation basis with ranibizumab. The submission had based the cost minimisation analysis on the treatment frequency in the Product Information for aflibercept (7 per year) and current practice based on PBS data for ranibizumab (8.8 per year). The PBAC considered it was uncertain whether less frequent

injections would eventuate with aflibercept treatment compared to ranibizumab treatment and recommended that the price of aflibercept be based on an injection: injection basis with ranibizumab. An analysis in the previous DUSC review, for a cohort of patients initiating treatment in the period December 2012 to November 2013, found a similar mean number of injections per patient in their first 12 months of treatment irrespective of whether aflibercept or ranibizumab was used.

The number of injections per patient by medicine prescribed for a more recent cohort (initiating in 2015) is presented below. The analysis compares the number of injections per patient in both their first and second years of AMD treatment, by medicine prescribed.

Table 10: Initiated 1 January 2015 to 31 December 2015

	First 12 months of treatment			12 to 24 months of treatment		
Medicines received	**Number of patients new to AMD treatment (Jan 15 to Dec 15)**	**Mean number of injections per new patient in their first 12 months of treatment**	**Weighted mean number of injections**	**Number of these patients continuing treatment in next 12 months**	**Mean number of injections per patient 12-24 months of treatment**	**Weighted mean number of injections**
Aflibercept only	3,635	8.40	8.55	2,786	6.88	7.16
Aflibercept + ranibizumab	166	11.96		251	10.25	
Ranibizumab only	3,482	8.08	8.48	2,267	6.51	7.03
Ranibizumab + aflibercept	567	10.95		792	8.52	
Total	7,850*		8.52	6,096		7.09

*Excludes 1,255 patients who received treatment for more than one indication.

The number of injections per patient in each of the first two years of treatment is similar whether ranibizumab or aflibercept is prescribed.

A small proportion (9%) of patients who initiated in 2015 switched from aflibercept to ranibizumab or vice versa. The mean number of injections per patient is higher in patients who switch. This is probably because of an inadequate response to the first medicine and the need for more frequent injections (monthly for at least the first 3 months) when switching.

Proportion of use for bilateral treatment

The ranibizumab submission estimated bilateral treatment in 10% of patients, and data from DHS provided for the 2012 DUSC report indicated about 20%. The 2015 DUSC report noted bilateral use is increasing over time based on the proportion of prescriptions with an increased maximum quantity of injections. DUSC agreed but considered that this measure underestimates bilateral treatment as it only captures simultaneous bilateral use, whereas bilateral use may also include each eye treated consecutively or alternately.

This analysis is updated below. A prescription with a dispensed quantity of two suggests the injections may have been to treat both eyes at once or close together. A quantity of three or more suggests these patients were dispensed all of the repeats at once, under regulation 24.

Table 11: Proportion of prescriptions by quantity dispensed over time

	1	2	3 or more
2007	94.23%	5.77%	0.00%
2008	94.30%	5.68%	0.01%
2009	94.06%	5.93%	0.01%
2010	92.79%	7.21%	0.00%
2011	92.29%	7.71%	0.00%
2012	91.64%	8.36%	0.00%
2013	91.24%	8.75%	0.01%
2014	90.94%	9.04%	0.02%
2015	90.54%	9.46%	0.00%
2016	89.97%	10.03%	0.00%
2017	89.28%	10.71%	0.00%

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Table 11 shows that the proportion of supplied injections where an increased maximum quantity was authorised has increased over time. Increased maximum quantities of 2 injections are presumed to be for bilateral treatment.

Table 12 shows the calculated percentage of prescriptions that were supplied with an increased quantity of 2 or more, in each year of treatment, by the calendar year of initiation. It suggests that for patients remaining on treatment, the proportion of bilateral use within a group of initiating patients tends to increase with time.

Table 12: Percentage of AMD prescriptions with an increased maximum quantity, in each year of treatment, by the calendar year of initiation

	1	2	3	4	5	6	7	8	9	10
Initiated 2007	6%	8%	10%	11%	11%	11%	11%	11%	12%	14%
Initiated 2008	5%	7%	9%	10%	12%	13%	13%	13%	13%	
Initiated 2009	5%	7%	9%	10%	10%	12%	13%	14%		
Initiated 2010	6%	8%	10%	12%	13%	14%	15%			
Initiated 2011	5%	7%	10%	11%	13%	14%				
Initiated 2012	5%	7%	9%	11%	13%					
Initiated 2013	5%	7%	10%	12%						
Initiated 2014	6%	7%	10%							
Initiated 2015	6%	8%								
Initiated 2016	6%									

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

This is likely an underrepresentation of the total number of patients receiving bilateral treatment. Patients may have received bilateral treatment without being dispensed a quantity of two. This may include where they were treated in their second eye a few years after the first eye, if they are supplied two injections at the same time on two different prescriptions, or if their two eyes are treated on alternate months. Additionally, patients receiving treatment for AMD in one eye and DMO or RVO in the fellow eye are represented once in each indication specific dataset.

When the number of patients dispensed a quantity of two or more at least once in a year was analysed the results were similar. It suggested approximately 7% of patients had a quantity of more than one in 2007 and 2008, increasing to approximately 14% in 2017 (data not shown).

Age and state/territory of treated patients

Table 13 shows the average age and range for new patients starting treatment with ranibizumab or aflibercept each year. Figure 2 shows the distribution of ages for the 2008 and 2017 initiating cohorts.

Table 13: Age of patients receiving ranibizumab and aflibercept by year of initiation

	Mean	Range
Initiated 2007	80	33 - 102
Initiated 2008	80	27 - 102
Initiated 2009	80	41 - 102
Initiated 2010	80	37 - 102
Initiated 2011	80	28 - 102
Initiated 2012	80	43 - 102
Initiated 2013	80	49 - 103
Initiated 2014	80	39 - 101
Initiated 2015	79	20 - 102
Initiated 2016	79	19 - 104
Initiated 2017	79	20 - 104

There were 34 patients excluded from this analysis as their age was missing on their first prescription.
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

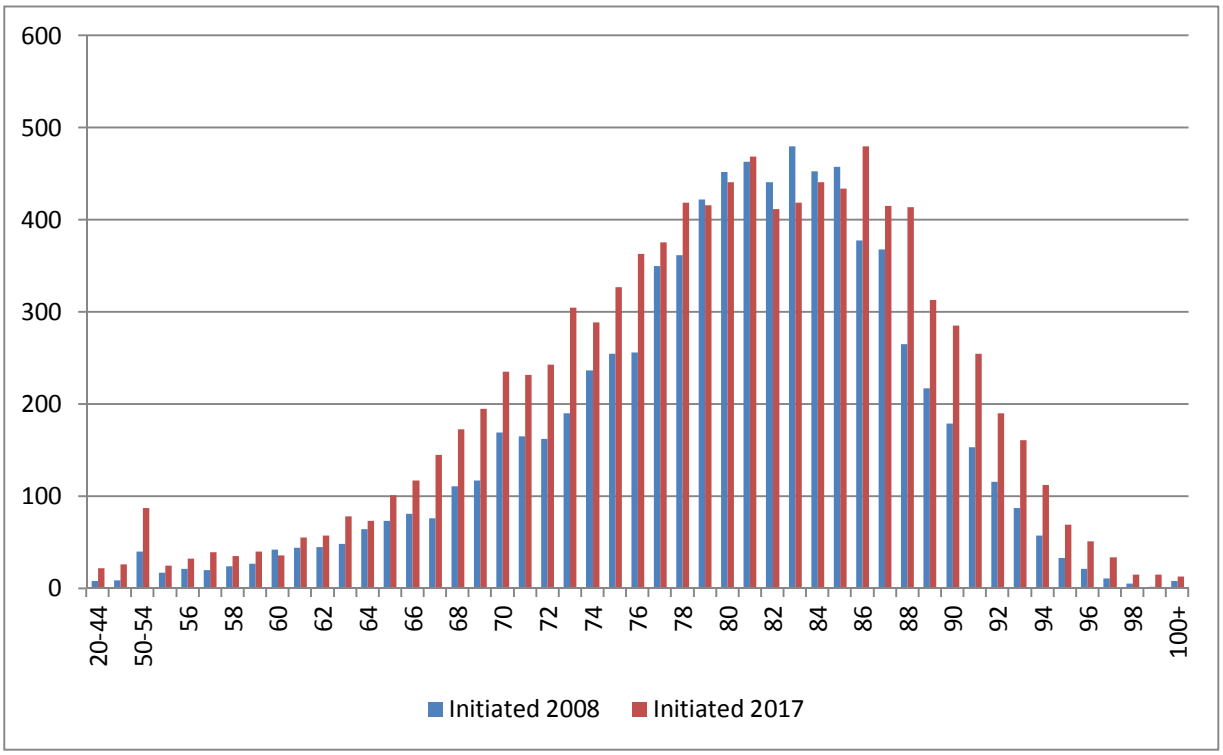

Figure 2: Age of patients initiating ranibizumab and aflibercept for AMD in 2008 and 2017, showing number of patients

There were 11 patients excluded from this analysis (six in 2008 and five in 2017) as their age was missing on their first prescription.
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

The mean age of the patient population who would receive treatment under the requested PBS indication was expected to be 77 to 78 years based on the clinical trial data. Prior to

2015 the mean age of patients initiating ranibizumab or aflibercept was 80. In 2015 to 2018 the mean age of patients initiating ranibizumab or aflibercept was 79.

Table 14 shows the number of people treated per 1000 population aged over 65 in each respective year.

Table 14: Patients receiving ranibizumab and aflibercept by year of treatment per 1000 population aged 65 or more by state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2007	6.03	4.53		3.86	2.34	4.74	3.16	2.60
2008	9.59	8.20	1.86	7.88	4.62	8.11	5.56	5.59
2009	12.03	10.40	2.93	10.15	6.85	10.00	7.06	7.85
2010	13.72	12.51	4.05	11.65	8.11	10.94	8.36	9.45
2011	15.79	14.02	4.72	13.09	9.02	13.03	8.95	11.14
2012	18.83	15.31	5.48	14.44	9.45	14.78	9.82	12.42
2013	21.09	17.00	6.06	16.07	10.97	16.17	11.10	13.57
2014	24.20	18.36	5.96	17.00	12.10	17.21	12.14	14.50
2015	25.56	19.73	7.92	17.68	12.75	17.97	13.13	15.67
2016	26.48	21.03	7.68	18.97	13.88	19.56	14.34	16.70
2017	28.31	22.27	11.22	21.02	15.18	21.16	15.72	18.30

Source: DHS Medicare Pharmacy Claims database, accessed March 2018
Patients with an 'unknown' state are excluded
Population: Australian Bureau of Statistics, 3101.0 - Australian Demographic Statistics, Jun 2017, Estimated Resident Population By Single Year Of Age, Year and State, Tables 51 to 58
http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Jun%202017?OpenDocument

There are differences in treatment rates across Australia. Rates of treatment are still comparatively lower in the Northern Territory and highest in the ACT, NSW, Tasmania and Queensland. States with a comparatively high number of people treated also tend to have the highest number of injections per patient as shown in the table below.

Table 15: Number of injections per patient by geographical state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2007	2.63	2.66		2.33	2.43	2.39	2.19	2.67
2008	5.21	5.08	3.44	3.77	3.97	4.22	3.78	4.53
2009	5.68	5.89	2.47	4.37	4.95	5.68	4.66	5.29
2010	6.88	6.72	3.64	5.60	5.92	6.77	5.47	5.98
2011	6.88	7.25	3.18	6.17	6.68	6.92	5.67	6.34
2012	7.13	7.71	4.56	6.48	7.13	7.80	5.84	6.52
2013	6.62	7.43	4.90	6.47	6.79	7.55	5.81	6.65
2014	6.83	7.33	5.90	6.45	6.81	7.48	6.06	6.51
2015	6.92	7.26	6.55	6.41	6.88	7.77	5.99	6.44
2016	6.67	7.30	6.66	6.55	6.79	7.58	6.07	6.45
2017	6.39	7.34	5.38	6.51	6.79	7.64	6.10	6.56

Source: DHS Medicare Pharmacy Claims database, accessed March 2018
Patients with an 'unknown' state are excluded

The 2015 DUSC report suggested possible reasons for the different rates of treatment could include access to ophthalmologists, remoteness and awareness of the disease and its symptoms. Overall, these results suggest that treatment rates could grow much more in the future if capacity increases or access improves, particularly in Victoria, South Australia and Western Australia. Table 15 suggests this has occurred, in Victoria, South Australia, Western Australia and Tasmania.

Analysis of medicines for DMO

Ranibizumab was the first medicine to be PBS listed for DMO, on 1 July 2015. Aflibercept was PBS listed four months later on 1 October 2015, and dexamethasone implants were listed 1 November 2016.

Figure 3 shows the number of patients initiating therapy for DMO. It suggests the number of initiating patients stabilised quickly, and the number of treated patients, although increasing, may be slowing or stabilising. It was anticipated that there was a pool of patients awaiting treatment prior to PBS subsidy. The depletion of this pool may be a factor contributing to the plateau. The use of dexamethasone could also be contributing to this apparent plateau in the numbers of prevalent patients treated in each calendar month given its less frequent administration.

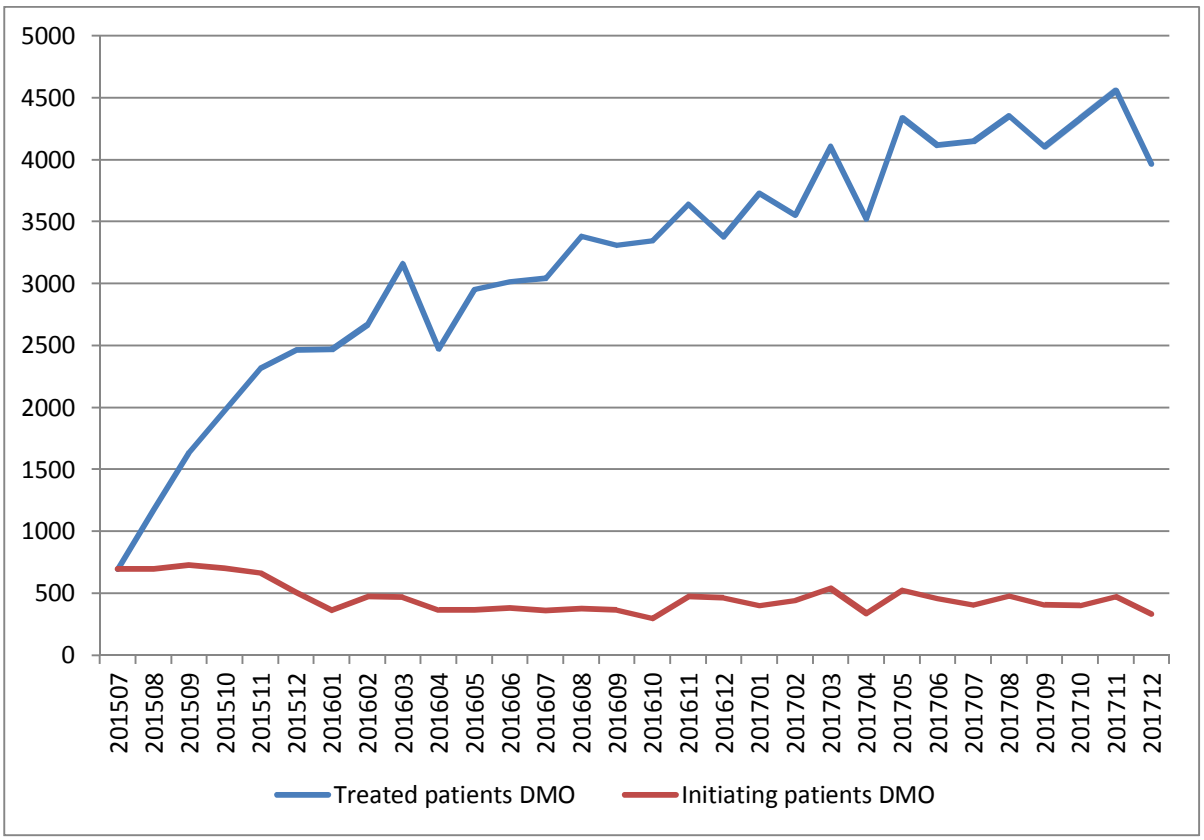

Figure 3: Initiating and prevalent treated patients for DMO

Since the listing of ranibizumab a total of 13,958 patients have been dispensed a medicine for DMO, including 12,934 who have received VEGF-inhibitor/s only and 546 patients who have received both a VEGF-inhibitor and dexamethasone.

A summary of the 13,480 patients who have received VEGF inhibitors for DMO is provided in Table 16. Dexamethasone prescriptions are excluded from Table 16 because of the different frequency of administration. Data on the use of dexamethasone is presented in a later section.

Table 16: Summary of patients accessing VEGF inhibitor treatment for DMO and number of supplied prescriptions, supplied injections and injections per patient by calendar year

Year	New patients	Rate of change from previous years new patients	Prevalent patients	Initiating patients per pop ≥18/1000	Treated patients per pop≥18/1 000	Prescriptions supplied	Injections supplied	Calculated injections per prevalent patient
2015[a]	3,990		3,990	0.216	0.216	11,888	15,720	3.94
2016	4,680	17%	8,248	0.249	0.439	43,114	56,341	6.83
2017	4,810	3%	11,137	0.252	0.583	55,193	70,408	6.32

Source: DHS Medicare Pharmacy Claims database, accessed March 2018
The figure for 2015 represents the first six months of listing for ranibizumab and the first three months of listing for aflibercept
[a] This cohort may also contain some patients who were treated prior to ranibizumab and aflibercept listing on the PBS, and therefore are not initiators to the therapy.

Injections per patient and continuation rates

The following tables represent the cohorts of patients who initiated in each calendar year. Individual patients were followed in 12 month periods from their initiation date. This analysis includes patients treated with dexamethasone and patients who have been treated for more than one indication (i.e. DMO and AMD or DMO and RVO).

Table 17: Number and percentage of patients remaining on treatment by initiating year

Patient numbers by initiating year and year of treatment

	Year 1	Year 2	Year 3
2015	3,990	2,938	1,751
2016	4,756	2,470	
2017	5,212		

Percentage of continuing patients from the number of initiators in year 1

	Year 1	Year 2	Year 3
2015	100.00%	73.63%	43.88%
2016	100.00%	51.93%	
2017	100.00%		

The majority of DMO patients continue into the second year of treatment, but the continuation rate in the third year is much lower based on data available since listing. The group of 2015 initiators possibly includes a prevalent pool of patients who had been treated prior to the PBS listing of ranibizumab, either with laser photocoagulation, off-label bevacizumab or privately supplied ranibizumab or aflibercept. This may impact on continuation rates.

The mean number of VEGF inhibitor injections per patient per year is provided in Table 18. Prescriptions of dexamethasone (due to its different frequency of administration) or patients who have been recorded as being treated for more than one indication are not included in the analysis.

Table 18: Average number of VEGF inhibitor injections supplied in each 12 months of therapy for patients by initiating year

	Year 1	Year 2
Initiated 2015	9.79	7.86
Initiated 2016	8.72	

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

[a] This cohort may also contain some patients who were grandfathered and therefore are not initiators to the therapy.

Number of injections per patient by medicine

The number of injections per patient in their first 12 months of DMO treatment is presented below according to the medicine prescribed. The PBAC recommended listing of aflibercept on a cost-minimisation basis to ranibizumab with a 1:1 injection ratio.

Table 19: Initiated 1 January 2016 to 31 December 2016

Medicines received	Number of patients new to DMO treatment (Jan 16 to Dec 16)	Mean number of injections per new patient in their first 12 months of treatment	Weighted mean number of injections
Aflibercept only	2,781	8.74	8.76
Aflibercept + ranibizumab	70	9.64	
Ranibizumab only	1,404	8.09	8.62
Ranibizumab + aflibercept	261	11.48	
Total		4,516	8.71

Note: excludes dexamethasone prescriptions

The number of injections per patient in the first 12 months of treatment is similar for aflibercept and ranibizumab. Similar to AMD, the mean number of injections per patient is higher in patients who switch, however these patients represent a small proportion of those who initiate (7%).

Proportion of use for bilateral treatment

Table 20: Proportion of VEGF inhibitor prescriptions by quantity dispensed over time

	1	2
2015	67.77%	32.23%
2016	69.32%	30.68%
2017	72.43%	27.57%

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Table 21: Percentage of prescriptions with an increased maximum quantity, in each year of treatment, by the calendar year of initiation

Row Labels	Year 1	Year 2	Year 3
2015	31%	31%	27%
2016	28%	29%	
2017	29%		

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

The proportion of prescriptions with increased quantities is much higher in DMO than AMD (approximately 30% compared to 5-15% for AMD). Note that patients treated for DMO in one eye and AMD in the other eye are represented once in each indication specific dataset.

As previously suggested by DUSC, the proportion of prescriptions with an increased quantity likely underestimates the true rate of bilateral treatment.

Age and state/territory of treated patients

Table 22 shows the average age and range of new patients starting treatment with ranibizumab or aflibercept for DMO. The distribution of age at initiation is provided in Figure 4.

Table 22: Age of patients receiving ranibizumab and aflibercept by year of initiation

	Mean (range)
Initiated 2015	64 (21 - 94)
Initiated 2016	64 (17 - 94)
Initiated 2017	65 (17 - 96)

There were 3 patients excluded from this analysis as their age was missing on their first prescription.
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

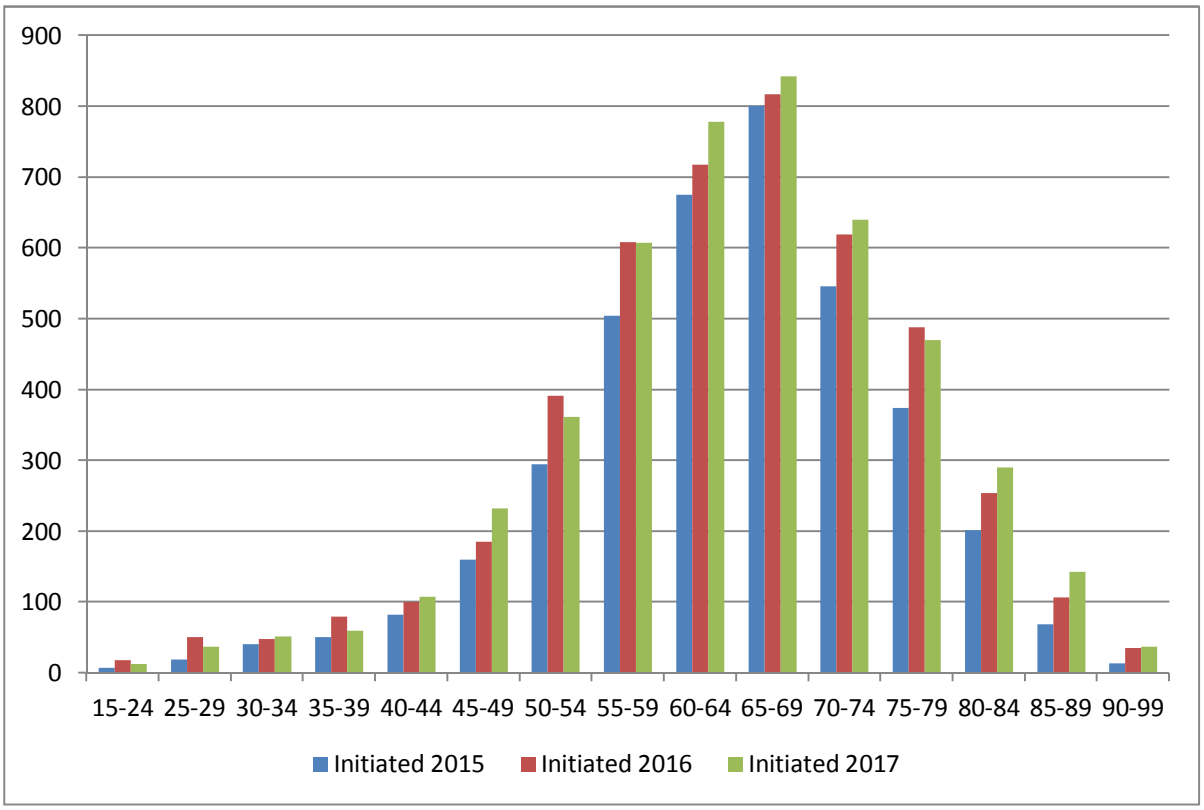

Figure 4: Age of patients initiating ranibizumab and aflibercept for DMO in 2015, 2016 and 2017, showing number of patients

The statistics and graph suggest the age of patients treated for DMO is younger than AMD consistent with the disease epidemiology.

Table 23 shows the number of treated patients, standardised by the estimated population 18 years or older in each state for the respective year. The geographical state of the patient is determined at their first prescription. The standardised figures suggest use is highest in Tasmania and NSW, and lowest in the NT. Table 24 also shows the number of injections per patient is highest in Tasmania and lowest in the NT.

It appears there is much more variation between states for DMO than AMD. The two indications were standardised differently (18 and above for diabetes and 65 and above for AMD), however the population standardised treatment rates for AMD ranged from 11.22 to 28.31 in 2017. The standardised treatment rates for DMO range from 13.65 to 81.33 in 2017. The range of rates for AMD are likely due to access, awareness, socioeconomic differences and patient affordability. The rates of treatment for DMO may also be affected by prevalence of diabetes, management of disease and screening for DMO.

Table 23: Patients receiving ranibizumab and aflibercept by year of treatment standardised by 100,000 population aged 18 or older by state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2015	15.89	32.78	3.84	10.72	18.67	30.06	17.93	11.99
2016	38.89	61.42	7.65	25.14	39.70	62.51	38.13	28.68
2017	52.39	73.99	13.65	41.95	53.18	81.33	51.03	45.16

Source: DHS Medicare Pharmacy Claims database, accessed March 2018
Patients with an 'unknown' state are excluded
Population: Australian Bureau of Statistics, 3101.0 - Australian Demographic Statistics, Jun 2017, Estimated Resident Population By Single Year Of Age, Year and State, Tables 51 to 58
http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Jun%202017?OpenDocument

Table 24: Number of injections per patient by geographical state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2015	3.41	4.42	2.71	3.58	3.54	3.84	3.37	3.47
2016	6.51	7.41	7.64	6.50	6.44	7.42	6.07	6.79
2017	6.13	6.89	5.60	6.03	6.26	7.12	5.67	5.99

Source: DHS Medicare Pharmacy Claims database, accessed March 2018
Patients with an 'unknown' state are excluded

Dexamethasone for DMO

The product information for dexamethasone implant notes that in the clinical trials most retreatments were administered between five and seven months after a prior treatment. Due to the less frequent treatment of dexamethasone, analysis of its use is presented separately below.

Figure 5 shows the number of patients initiating to dexamethasone implant and the number treated. These patients may have previously been treated with VEGF inhibitors.

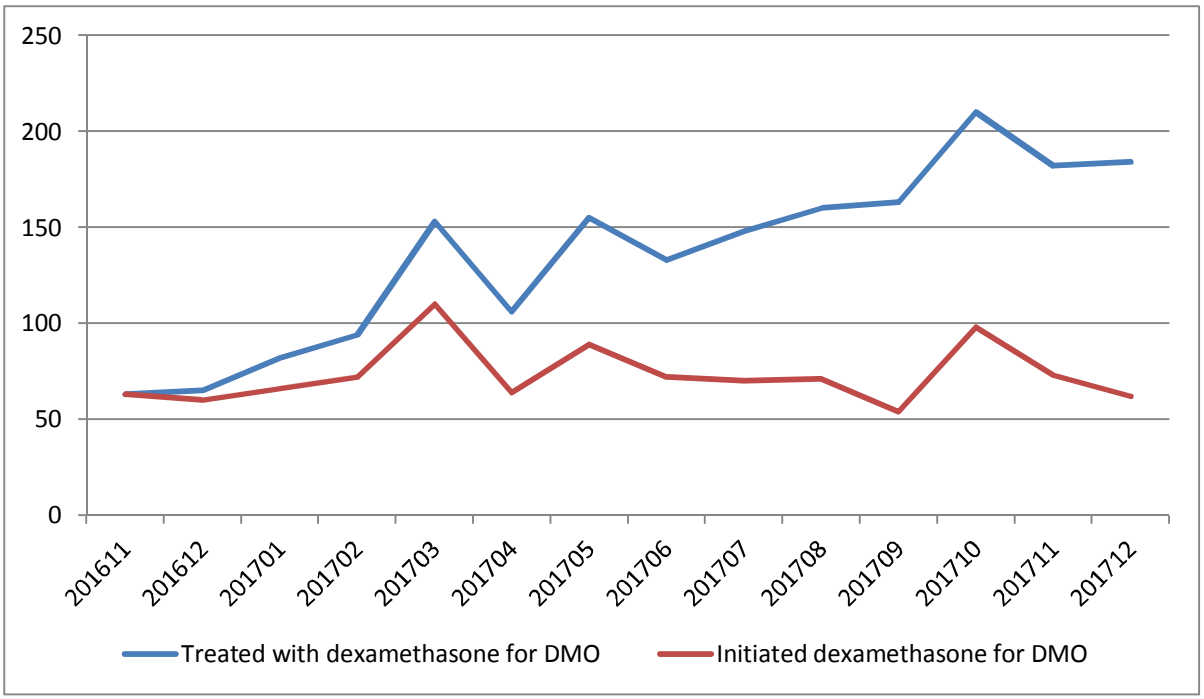

Figure 5: Patients initiated and treated with dexamethasone for DMO

The number of treated patients does not appear to have increased as quickly as other treatments for DMO, although this is affected by the longer retreatment time. As this report includes 14 months of dexamethasone implant data, it is difficult to know whether the number of initiating patients will increase, or if the number of treated patients will trend upwards as patients are retreated.

Table 25: Summary of patients accessing treatment for dexamethasone for DMO and number of supplied prescriptions, supplied injections and injections per patient by calendar year

Year	New patients	Prevalent patients	Initiating patients per pop ≥18/1000	Treated patients per pop≥18/1000	Prescriptions supplied	Injections supplied	Calculated injections per prevalent patient
2016	123	123	0.008	0.008	131	165	1.34
2017	901	995	0.056	0.062	1,870	2,197	2.21

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

The use of dexamethasone for DMO represents a small proportion of the market for DMO. In 2017 11,137 patients were supplied 70,408 injections of either aflibercept or ranibizumab, while 995 patients were supplied 2,197 dexamethasone implants. Use of dexamethasone is likely still increasing as it has only been listed since 1 November 2016.

The rates of bilateral treatment with dexamethasone based on quantity per prescription is presented in Table 26.

Table 26: Proportion of prescriptions by quantity dispensed over time

Year	1	2
2016	74.05%	25.95%
2017	82.51%	17.49%

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

The proportion of prescriptions dispensed with a quantity of 2 is lower for dexamethasone implants for DMO than for ranibizumab and aflibercept for DMO. This may be because the product information for dexamethasone implants states that administration in both eyes on the same day is not recommended. An analysis using MBS data could determine if patients receiving bilateral treatment are having the implants administered on the same or different days, but this was considered beyond the scope of the current report.

The PBS restriction for dexamethasone limits use to patients unsuitable for, contraindicated to, or who have failed VEGF inhibitors. For the 1,024 patients who have been supplied dexamethasone for DMO, the 10 most common drug sequences are shown in Table 27. In total 506 patients were supplied dexamethasone before any other medicine for DMO.

When this analysis was repeated using the complete dataset (including prescriptions for AMD and RVO), 450 patients were supplied dexamethasone who had never been supplied aflibercept or ranibizumab, and 477 patients were initiated on dexamethasone.

Given the number of patients initiating on dexamethasone, it is likely the PBAC was correct to note that there would be no cost offsets for patients unsuitable for VEGF inhibitors and that there would be some growth in the current market rather than cost savings from substitution for VEGF inhibitors.

Table 27: Top 10 drug sequences for DMO which include dexamethasone

Sequence	Patient count
DEXAMETHASONE	478
AFLIBERCEPT, DEXAMETHASONE	181
RANIBIZUMAB, DEXAMETHASONE	84
RANIBIZUMAB, AFLIBERCEPT, DEXAMETHASONE	67
AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT	46
AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT, DEXAMETHASONE	26
DEXAMETHASONE, AFLIBERCEPT	17
RANIBIZUMAB, AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT	13
AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT	12
AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT, DEXAMETHASONE, AFLIBERCEPT, DEXAMETHASONE	11

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Analysis of ranibizumab and aflibercept for RVO

Ranibizumab and aflibercept are now both listed for CRVO and BRVO. Figure 6 shows the number of patients initiating to and on treatment for RVO.

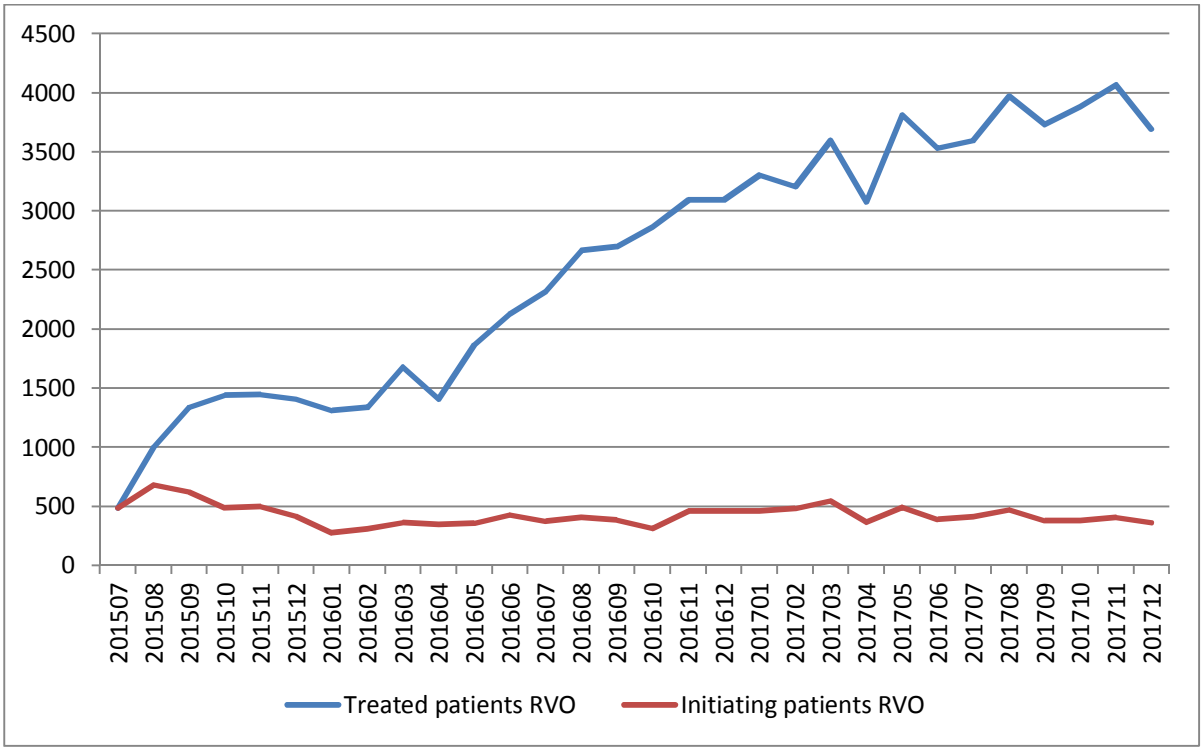

Figure 6: Initiating and prevalent treated patients for CRVO and BRVO

The number of initiating patients has quickly stabilised. The number of treated patients initially increased and then was very stable between October 2015 and April 2016 before increasing again. Aflibercept was PBS listed for CRVO in October 2015 and BRVO in December 2016, which does not explain the increase in treated patients from May 2016. It is more likely due to patients being treated who had already been treated outside of the PBS either by laser photocoagulation or non-PBS medicines finishing their treatment. The slowly increasing number of treated patients likely represents patients truly initiating therapy on the PBS.

Table 28: Summary of patients accessing treatment for RVO and number of supplied prescriptions, supplied injections and injections per patient by calendar year

Year	New patients	Rate of change from previous years new patients	Prevalent patients	Initiating patients per pop ≥40/1000	Treated patients per pop≥40/ 1000	Prescriptions supplied	Injections supplied	Calculated injections per prevalent patient
2015	3,191[a]		3,191	0.288	0.288	7,784	7,904	2.48
2016	4,474	40%	7,118	0.398	0.633	29,010	29,350	4.12
2017	5,137	15%	10,781	0.450	0.944	47,376	48,040	4.46

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

[a] part year – ranibizumab was listed 1 July 2015 for BRVO and CRVO; aflibercept listed 1 October 2015 for CRVO and 1 December 2016 for BRVO

In total 12,802 patients have been treated for BRVO or CRVO. Of the 12,802 patients who have been treated for BRVO or CRVO, 5,023 were also recorded as being treated for AMD or DMO. The estimates for BRVO and CRVO did not account for patients with comorbidities of RVO and AMD/DMO, however it cannot be determined if this use is in patients with multiple conditions, or use outside of the PBS restriction prior to RVO listing.

Of the remaining 7,780 patients who were only treated for RVO, 4,590 (59%) were only treated for BRVO, 2,999 (39%) were only treated for CRVO, and 190 (2%) were treated for both BRVO and CRVO. The following analyses use only the 7,590 patients treated for either BRVO or CRVO only.

Injections per patient and continuation rates

Table 29: Number and percentage of patients remaining on treatment by initiating year

Patient numbers by initiating year and year of treatment

BRVO				CRVO			
	Year 1	Year 2	Year 3		Year 1	Year 2	Year 3
2015	760	414	222	2015	453	240	128
2016	1,451	686		2016	1,073	501	
2017	2,380			2017	1,473		

Percentage of continuing patients from the number of initiators in year 1

BRVO				CRVO			
	Year 1	Year 2	Year 3		Year 1	Year 2	Year 3
2015	100%	54%	29%	2015	100%	53%	28%
2016	100%	47%		2016	100%	47%	
2017	100%			2017	100%		

For both BRVO and CRVO about half of patients remain on treatment in the second year, and about 30% in the third year. The proportion of patients ceasing treatment due to resolution or lack of improvement cannot be ascertained from prescription data. It has been noted that BRVO can spontaneously resolve.

Table 30: Average number of injections supplied in each 12 months of therapy for patients by initiating year

BRVO			CRVO		
	Year 1	Year 2		Year 1	Year 2
Initiated 2015	5.10	4.95	Initiated 2015	5.13	5.09
Initiated 2016	6.22		Initiated 2016	5.88	

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

[a] This cohort may also contain some patients who were grandfathered and therefore are not initiators to the therapy.

The mean number of injections for RVO is lower than for AMD or DMO, likely due the low rates of bilateral treatment in RVO.

Number of injections per patient by medicine

The number of injections per patient in their first 12 months of RVO treatment by medicine prescribed is presented below. Note that ranibizumab listed July 2015 for CRVO and BRVO, aflibercept listed October 2015 for CRVO and December 2016 for BRVO.

Table 31: Initiated 1 January 2016 to 31 December 2016

Medicines received	Number of patients new to RVO treatment (Jan 16 to Dec 16)	Mean number of injections per new patient in their first 12 months of treatment	Weighted mean number of injections
Aflibercept only	664	5.76	5.84
Aflibercept + ranibizumab	13	10.15	
Ranibizumab only	1,659	5.86	6.24
Ranibizumab + aflibercept	264	8.59	
Total	2,600		6.13

Source: DHS Medicare Pharmacy Claims database, accessed March 2018, includes patients who have been treated for BRVO, CRVO or both, but not for AMD or DMO.

This analysis was attempted separately for BRVO and CRVO, however the patient numbers were too small to present. The number of patients treated for either BRVO or CRVO who switch from aflibercept to ranibizumab is very small (around 1 to 2%). The number who switch from ranibizumab to aflibercept is around 15%, although around 75% of people in the cohort initiated on ranibizumab. This is consistent with the listing dates of these medicines.

Proportion of use for bilateral treatment

Table 32: Proportion of prescriptions by quantity dispensed over time

BRVO			CRVO		
	1	2 or more		1	2 or more
2015	98.72%	1.28%	2015	98.27%	1.73%
2016	99.15%	0.85%	2016	98.67%	1.33%
2017	99.37%	0.63%	2017	98.89%	1.11%

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Table 33: Percentage of prescriptions with an increased maximum quantity, in each year of treatment, by the calendar year of initiation

BRVO				CRVO			
	1	2	3		1	2	3
Initiated 2015	1.5%	1.9%	2.0%	**Initiated 2015**	2.0%	2.7%	2.3%
Initiated 2016	0.6%	0.3%		**Initiated 2016**	0.9%	1.2%	
Initiated 2017	0.3%			**Initiated 2017**	0.9%		

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Table 32 and 33 show that the rates of increased maximum quantities are much lower in RVO than in AMD or DMO, and prescriptions for RVO are nearly always dispensed with a quantity of one. This is consistent with expectations of RVO, that it is a unilateral disease which generally affects one eye at a time.

Age and state/territory of treated patients

Table 34 shows the average age and range of new patients starting treatment with ranibizumab or aflibercept for RVO.

Table 34: Age of patients receiving ranibizumab and aflibercept by year of initiation

	Mean (range)
Initiated 2015	73 (18 - 99)
Initiated 2016	72 (19 - 99)
Initiated 2017	73 (18 - 101)

There were 4 patients excluded from this analysis as their age was missing on their first prescription.
Source: DHS Medicare Pharmacy Claims database, accessed March 2018, includes patients who have been treated for BRVO, CRVO or both, but not for AMD or DMO

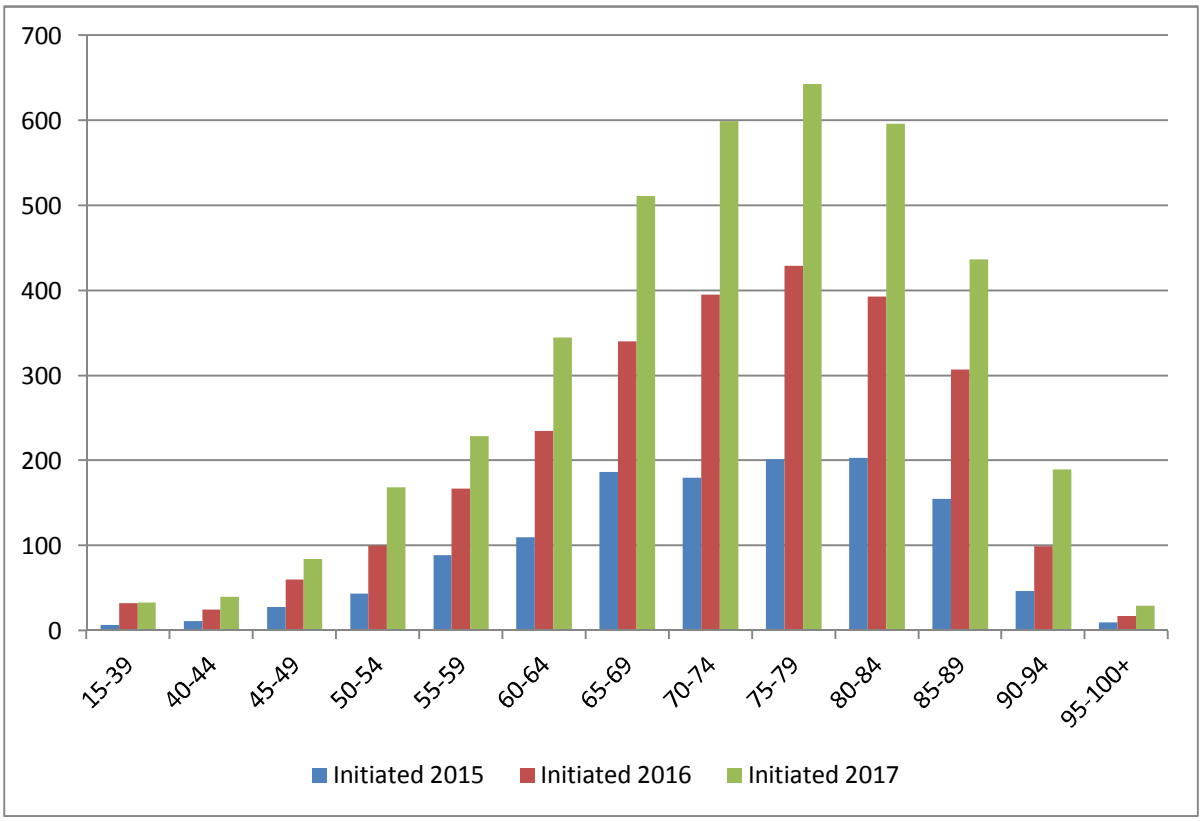

Figure 7: Age of patients initiating ranibizumab and aflibercept for RVO in 2015, 2016 and 2017, showing number of patients

Includes patients who have been treated for BRVO, CRVO or both, but not for AMD or DMO

The increasing numbers in each calendar year reflect the growing number of initiating patients, however the distribution appears similar in each year of listing. For RVO the mean age of initiating patients is 73 or 74, which is older than the patients in the CRVO and BRVO clinical trials considered by the PBAC, who were around 65 years of age. For the COPERNICUS (Brown et al., 2013) and GALILEO (Holz et al., 2012) trials, the mean patient age was 66.3 and 61.5 years, respectively. The BRAVO (Campochiaro et al., 2010) and CRUISE (Heier et al., 2012) trials were presented in the ranibizumab submissions with the mean ages for the trial groups ranging from 65.2 to 71 years, respectively.

The rates of treatment and injections per patient by geographical state of the patient determined at their first prescription are presented in Tables 35 and 36.

Table 35: Patients receiving ranibizumab and aflibercept by year of treatment standardised by 100,000 population aged 40 or older by state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2015	13.81	14.71	2.20	8.41	13.00	18.24	11.15	5.90
2016	31.87	39.08	5.44	23.42	34.22	45.79	31.57	24.09
2017	64.70	66.93	8.62	49.14	64.68	76.45	52.47	47.23

Source: DHS Medicare Pharmacy Claims database, accessed March 2018, includes patients who have been treated for BRVO, CRVO or both, but not for AMD or DMO
Patients with an 'unknown' state are excluded
Source: Estimated resident population, by sex and age groups–States and territories–at 30 June 2017, ABS 31010DO001_201409 Australian Demographic Statistics, Release 14 December 2017, Table 7, http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Jun%202017?OpenDocument

Similar to DMO, the treatment rate for RVO is highest in Tasmania and lowest in the Northern Territory. The disparity in treatment rates in the Northern Territory compared to other states/territories seems more pronounced for RVO than DMO or AMD. This may be due to remoteness and the importance of early treatment of CRVO. Western Australia and Queensland also have lower treatment rates for RVO compared with other states, also suggesting remoteness may be a factor affecting treatment rates.

Table 36: Number of injections per patient by geographical state

Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
2015	2.26	2.32	1.50	2.07	2.03	2.22	2.04	2.06
2016	4.11	4.24	4.20	3.94	4.14	4.06	3.63	3.77
2017	4.19	4.58	4.13	4.19	4.66	5.01	4.03	4.15

Source: DHS Medicare Pharmacy Claims database, accessed March 2018, includes patients who have been treated for BRVO, CRVO or both, but not for AMD or DMO
Patients with an 'unknown' state are excluded

The number of injections per patient is also highest in Tasmania, however in 2016 the Northern Territory and NSW were the highest.

Patients treated for more than one indication

The analyses presented in previous sections largely included patients who had only been treated for one indication. The table below summarises the number of patients treated for one or more than one indication. In total, between August 2007 and December 2017, 108,124 patients were treated for one indication, 5,557 for two, and 479 had no indication on any of their prescriptions. These 479 mostly represent veterans who were supplied medicines using the '1996' authority code.

Table 37: Number of patients treated for one or more than one indication

Indication 1	Indication 2	Patient Count
AMD	.	86,580
AMD	BRVO	721
AMD	CRVO	1,035
AMD	DMO	171
BRVO	.	4,590
BRVO	AMD	1,815
BRVO	CRVO	149
BRVO	DMO	30
CRVO	.	2,999
CRVO	AMD	1,292
CRVO	BRVO	95
CRVO	DMO	30
DMO	.	13,476
DMO	AMD	181
DMO	BRVO	21
DMO	CRVO	17
nil	.	479
Total		113,681

Overall utilisation

Combining all patients who have received treatment for AMD, DMO, RVO or two of the three, Figure 8 shows the total number of patients starting treatment with PBS subsidised aflibercept, ranibizumab or dexamethasone implants for the first time (initiating), and the total number of patients receiving treatment with aflibercept, ranibizumab or dexamethasone implants (prevalent).

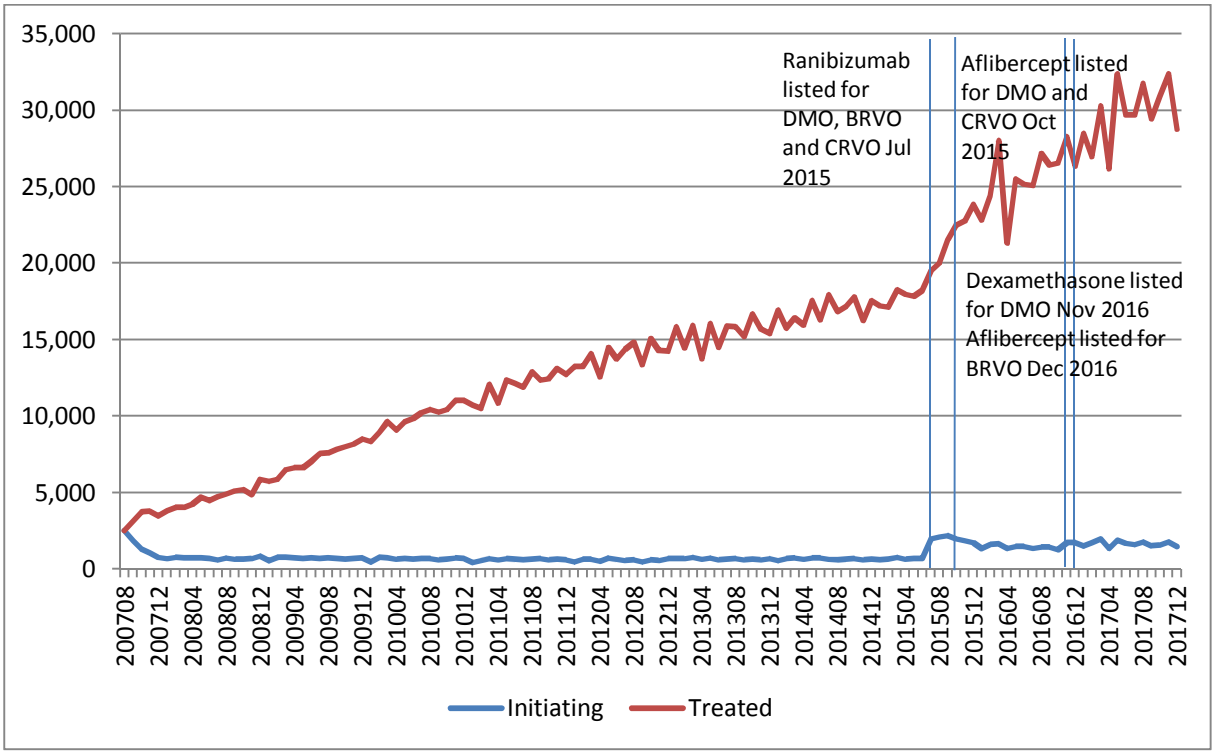

Figure 8: Number of initial patients and all patients treated each month from August 2007 to December 2017

Source: DHS Medicare Pharmacy Claims database, accessed March 2018

This figure shows the impact of the new listings for DMO and RVO in mid-2015, and the related inflection in the number of prevalent treated patients. In 2014 15, 272 patients initiated to one of these medicines, in 2017 39,328 patients initiated. It also shows that the number of prevalent treated patients continues to grow.

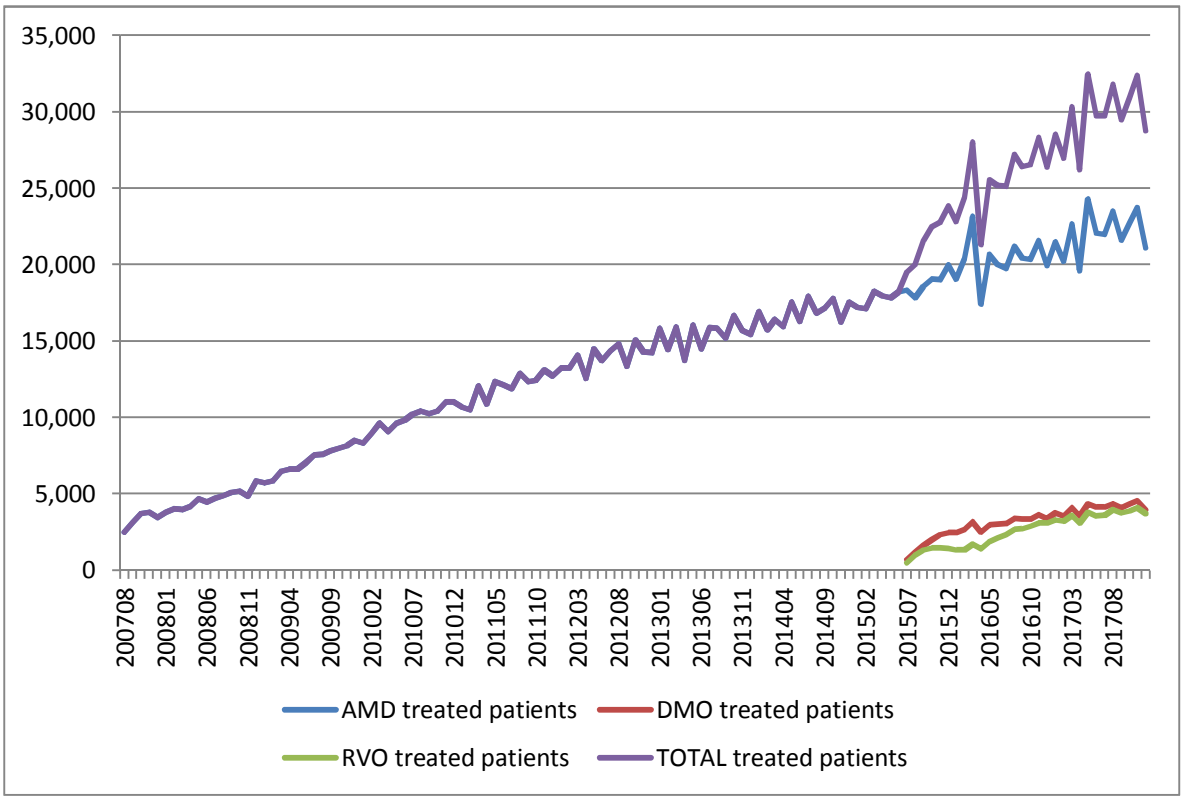

Figure 9: Number of treated patients each month from August 2007 to December 2017
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

Figure 9 shows the number of treated patients by indication since 2007. Use for AMD is approximately 75% of the total market. Use for DMO and RVO is similar.

Figure 10 shows the number of injections (solid line) and number of prescriptions (broken line) for medicines used to treat AMD, RVO and DMO. The usual maximum quantity per prescription is one injection of either aflibercept or ranibizumab, but some prescriptions are authorised for an increased maximum quantity.

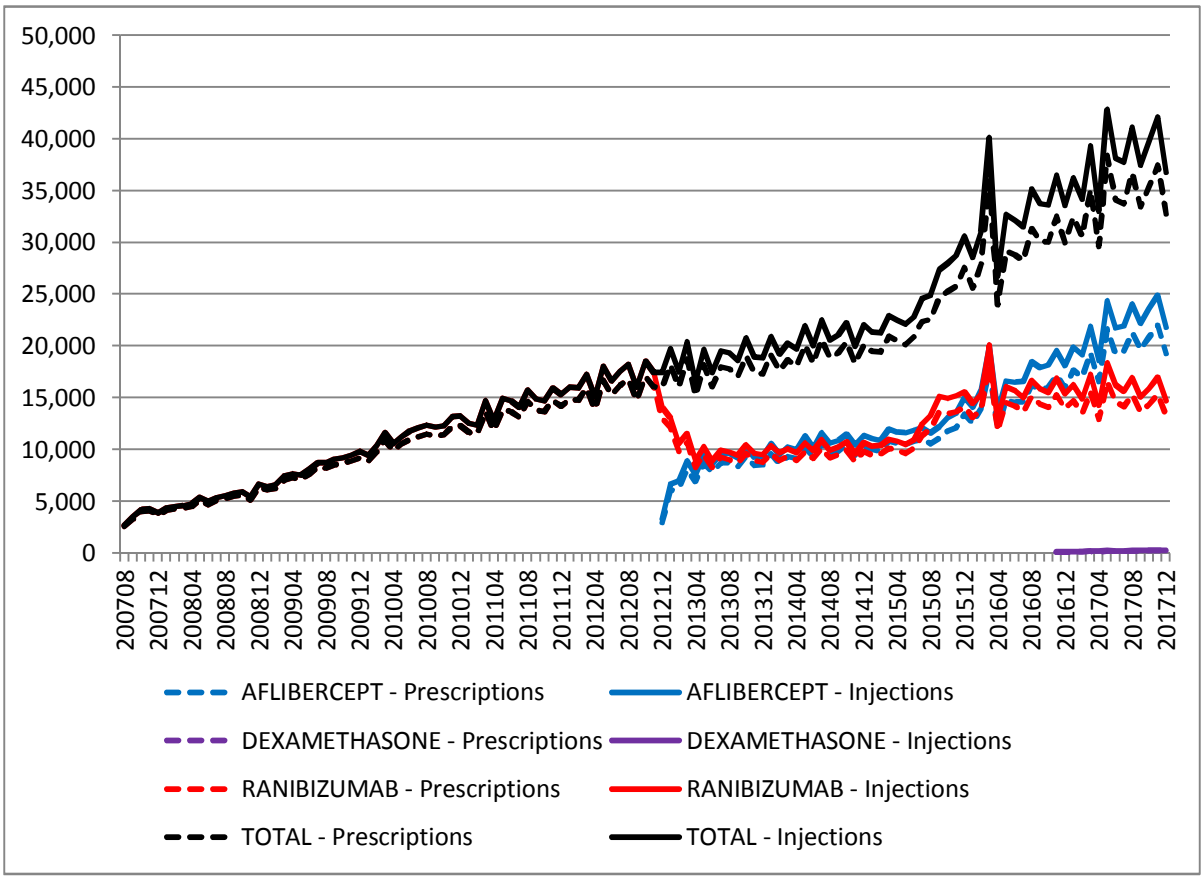

Figure 10: Prescriptions and supplied injections for ranibizumab, aflibercept, dexamethasone implant, from August 2007 to December 2017
Source: DHS Medicare Pharmacy Claims database, accessed March 2018

The total number of prescriptions has increased steadily over the past ten years. The increase may have been slowing prior to 2015, but following the listing of ranibizumab and then aflibercept for DMO and RVO utilisation increased further. In the 2015 report it was noted that the use of ranibizumab and aflibercept each had approximately 50 percent market share. It appears that ranibizumab has been stable during 2016 and 2017, while the use of aflibercept continues to grow. As noted in the 2015 report, there is a small but increasing divergence between the number of injections and prescriptions over time.

In 2017 there were 1,882 prescriptions supplied for dexamethasone implant. As previously noted, use of dexamethasone for DMO is a small proporion of the market for DMO. Use of dexamethasone implant is low and may be stabilising at approximately 200 prescriptions per month dispensed.

Proportion of use for bilateral treatment

The 2015 report stated, "As authority approval for initial treatment of each eye must be sought, and the first authority application for each eye must be made in writing or by telephone, a more recent assessment of the extent of bilateral treatment with PBS subsidised aflibercept and ranibizumab may be possible from the DHS authority approval data."

The Secretariat has requested data from DHS regarding the proportion bilateral use. DHS was able to supply this data relating to AMD, DMO and RVO authority approvals for ranibizumab, aflibercept and dexamethasone in the 2017 calendar year. This is summarised below for overall proportion rather than by indication.

Right Eye	30,903
Left Eye	30,564
Both Eyes	9,100
Total patients	58,874

Source: DHS authority approvals

The figures do not equate to the total patients as one patient may have received approval for left eye and right eye on separate occasions. Additionally, it underestimates the total amount of bilateral treatment because if a patient has received left eye, then right eye then both eyes, they would only show in the categories that have been approved in 2017.

Analysis of actual versus predicted utilisation

Ranibizumab – DMO

The resubmission took a prevalence approach to estimating the number of people eligible for treatment with ranibizumab. The estimated size of the diagnosed Australian diabetic population was based on ABS estimates and AIHW prevalence estimates projected to 2018 (4.4% of the total Australian population in 2007/08). It assumed 5.6% of these patients have macular oedema (Diabetic Retinopathy in Victoria, Australia (2000)). Previous submissions estimated 9.3% of DMO patients would have visual impairment.

DUSC (February 2013 and October 2013) considered a significant uncertainty was the amount of overlap between patients with DMO and patients with visual impairment. DUSC therefore requested sensitivities of the financial estimates if the percentage with visual impairment was approximately three times higher (25%) and five times higher (50%). The July 2014 resubmission estimated 25% of diabetic patients with DMO would have visual impairment.

Patients were assumed to initiate ranibizumab from the prevalent pool in Year 1, and then from the 'prevalent pool less previously initiated patients' in subsequent years. The submission assumed an uptake of 50% of the total pool in Year 1, rising steadily to a maximum of 80% by Year 4.

Based on the results of the RESTORE trial, the November 2013 submission assumed 62.5% of patients initiated to ranibizumab for DMO would respond to treatment. DUSC (June 2013) considered it likely that the interpretation of a response may be higher in clinical practice than in the RESTORE trial and requested a sensitivity analysis based on 75% response rate. The July 2014 resubmission assumed 75% of initiators would respond.

Treatment continuation rates for responders were estimated based on the continuation rates in the RESTORE trial and the RESTORE Extension Study. The resubmission assumed 88% of initiators who responded to treatment would continue treatment during the second year after initiation, and 88% of these patients would continue treatment during the third year after initiation. Multiplying response rate (75%) with the continuation rate of responders (88%) this assumes 66% of initiators would continue in the second year after initiation, and 58% of initiators would continue in the third year. The November 2013 submission assumed treatment continuation rates from Years 3-4 and 4-5 to be 50% and 30% respectively, however the July 2014 submission did not include any treatments for patients in fourth or fifth years of treatment, as the economic model limited treatment duration to three years. The final agreed estimates included continuation rates of 68%, 48% and 28% for patients moving from years 3 to 4, years 4 to 5 and years 5 to 6 and more respectively.

The predicted number of injections administered to patients were also based on the RESTORE trial and the RESTORE Extension Study. These are summarised in Table 38.

Table 38: Predicted number of injections administered per patient of ranibizumab for DMO

Year of treatment	Avg injections per eye (initiations responders)	Avg injections per eye (initiations non-responders)	% of patients treated bilaterally	Avg injections per patient (responders)	Avg injections per patient (non-responders)
Year 1	7.0	3.0	20%	8.4	3.6
Year 2	3.9		50%	6.8	
Year 3	2.9		80%	6.8	
Year 4	2.9		80%	5.5	
Year 5	2.9		80%	5.2	

Source: Ranibizumab DMO submission July 2014, Section E DME_Utilisation and Financial Estimates_FINAL.xlsx, 'Background and Assumptions' tab

The submission assumed the responders (75% of initiators) would receive an average of 8.4 injections and non-responders (25% of initiators) would receive an average of 3.6 injections. Overall these assumptions estimated initiators would receive 7.2 injections.

As ranibizumab was PBS listed for DMO before aflibercept, the final agreed estimates estimated the entire DMO market. The actual numbers below include all patients and treatments for DMO.

Table 39: Ranibizumab actual versus predicted utilisation for DMO

	Year 1	Year 2	Year 3	Year 4	Year 5
	2015	2016	2017	2018	2019
Predicted initiating DMO patients	9,596	6,322	5,908	5,140	5,260
Actual total initiating DMO patients	3,990	4,756	5,212		
Difference	-58%	-25%	-12%		
Predicted total DMO patients	9,596	12,650	15,642	16,486	16,385
Actual total treated DMO patients	3,990	8,326	11,716		
Difference	-58%	-34%	-25%		
Utilisation estimates - total injections	34,547	89,371	109,253	109,829	108,014
Actual total injections for DMO (including dexamethasone)	15,720	56,506	72,605		
Difference	-54%	-37%	-34%		

Source: PBS Ranibizumab vD 20150424.xlsx, DME 'Epidemiology and Patient Number' tab

The predictions for the number of people commencing and on treatment with ranibizumab for DMO were overestimated. It is not clear whether this is due to an overestimate of the number of people eligible for treatment given there was very little information available on the proportion of patients with diabetes and DMO with VI, or an overestimate of treatment uptake. Both were uncertain. The difference between predicted and actual patients was

smaller for initiating patients in 2016 and 2017 than treated patients. This may suggest the continuation rates were overestimated (discussed in more detail below).

The overall number of injections was also lower than expected primarily due to the overestimated number of people eligible for and taking up treatment. However the following factors have also contributed to differences in the number of injections used in practice:

- The rate of bilateral treatment was overestimated. The submission assumed 20% of patients would be treated bilaterally in year 1, 50% in year 2, and 80% in years 3 to 5. Tables 20 and 21 show the proportion of prescriptions dispensed with a quantity of two has been approximately 30% and has decreased slightly since 2015. The true rate of patients with bilateral disease is likely higher than the rate of prescriptions dispensed with a quantity of two, due to patients being treated in different eyes on different days or having disease in both eyes but one eye not needing treatment every month.
- The second year continuation rates were underestimated. The submission assumed 66% of initiators would continue in the second year after initiation. Table 17 showed that of patients who initiated in 2015, 74% were also treated in 2016, and of patients who initiated in 2016, 52% were also treated in 2017. Further, the submission assumed 58% of initiators would continue in the third year after initiation. Table 17 shows that of patients who initiated in 2015, 44% were also treated in 2017. The PBS restriction criteria do not include stopping or continuation criteria. It is unclear if patients are not continuing with treatment because they have received good results, or failed treatment.
- The number of injections per patient was underestimated. Overall the submission estimated initiators would receive 7.2 injections in year 1. Table 18 shows that the average number of injections supplied in each 12 months of therapy was 9.79 and 8.72 for patients who initiated in 2015 and 2016 respectively. These findings indicate that there were more actual injections per patient. However, it should be noted that the projected and actual results are not directly comparable because the estimates were derived for a particular calendar year while the actual number of injections is for therapy over a 12 month period from the date of initiation.

Overall it appears the rate of bilateral treatment was underestimated in the early years of listing, the second year continuation rates were underestimated, and the number of injections per patient was underestimated. However, the number of patients was substantially overestimated in the early years of the PBS listing, although the overestimate appears to be decreasing over time.

Aflibercept - DMO

[redacted]

Table 40: Predicted number of injections administered per initiator on aflibercept for DMO

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 41: Aflibercept actual versus predicted utilisation for DMO

	Year 1	Year 2	Year 3	Year 4	Year 5
	2015	2016	2017	2018	2019
Predicted treated DMO patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual total treated DMO patients	3,990	8,326	11,716		
Difference	[redacted]	[redacted]	[redacted]		
Utilisation estimates - total injections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual total injections for DMO (including dexamethasone)	15,720	56,506	72,605		
Difference	[redacted]	[redacted]	[redacted]		

[redacted]

[redacted]

[redacted]

Dexamethasone – DMO

The submission for dexamethasone implant for DMO used an epidemiological approach to estimate its use. [redacted]

It estimated patients in the first year of treatment would have 2.76 treatments per year, patients in the second year of treatment would have 1.92 treatments per year, and patients in the third to fifth years of treatment would have 1.8 treatments per year.

A detailed predicted versus actual analysis of dexamethasone was not undertaken as it has only been listed on the PBS since 1 November 2016 and has a comparatively small market share. The results section provides some information about utilisation of dexamethasone to assist in interpretation of the overall utilisation of medicines for DMO.

Ranibizumab - RVO

The submission for ranibizumab for RVO used an epidemiological approach to estimate the use of ranibizumab for CRVO and BRVO. It applied incidence and prevalence rates from the Blue Mountains Eye Study 2010 to the estimated Australian population aged 40 and older. The submission assumed different proportions of BRVO and CRVO patients would have visual impairment (Prevalent: BRVO: 35.7%, CRVO: 75%; Incident: BRVO: 12.5%, CRVO: 55.6%).

The submission applied a bilateral treatment rate of 5% to the estimates for BRVO and CRVO. The submission stated the clinical trials did not capture the rate of bilateral treatment, so this assumption was based on clinician feedback.

The response rates were estimated from the BRAVO and CRUISE trials, the continuation rates were estimated from the number of patients continuing from BRAVO/CRUISE to HORIZON extension study, and the average numbers of injections were also estimated from the BRAVO and CRUISE trials.

Table 42: Continuation rates and predicted number of injections administered per patient of ranibizumab for RVO

	Injections/patient	
	BRVO	**CRVO**
Response rate to initial therapy	60.3%	50.8%
Proportion continuing into Yr 2	63%	79%
Proportion continuing on therapy into Yr 3	70%	52%
Proportion continuing on therapy post-Yr 3	70%	52%
Initiations: Responders	8.4	8.9
Initiations: Non-responders	4	4
Year 2 continuations	4.2	4.6
Year 3+ continuations	2	2

Source: Ranibizumab RVO submission November 2014, Usage and financial estimates - RVO_Final.xlsx, 'Background and Assumptions' and 'Epidemiology and Patient Number' tabs

As ranibizumab was PBS listed for RVO before aflibercept, the final agreed estimates estimated the entire RVO market.

Table 43: Ranibizumab actual versus predicted utilisation for RVO

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients treated per year					
BRVO					
Predicted	2,033	1,965	2,294	2,600	2,803
Actual	1,934	4,148	6,211		
Difference	-5%	+111%	+171%		
CRVO					
Predicted	3,768	3,452	3,955	4,292	4,553
Actual	1,286	3,099	4,799		
Difference	-66%	-10%	+21%		
Total					
Predicted	5,800	5,417	6,249	6,892	7,356
Actual	3,191	7,118	10,781		
Difference	-45%	+31%	+73%		
Total number of injections					
BRVO					
Predicted	14,201	11,737	12,212	13,481	14,115
Actual	4,817	16,957	27,634		
Difference	-66%	+44%	+126%		
CRVO					
Predicted	27,512	21,670	21,757	22,817	23,592
Actual	3,087	12,393	20,406		
Difference	-89%	-43%	-6%		
Total					
Predicted	41,714	33,407	33,968	36,298	37,707
Actual	7,904	29,350	48,040		
Difference	-81%	-12%	+41%		

Source: PBS Ranibizumab vD 20150424.xlsx, RVO 'Epidemiology and Patient Nu (2' tab

Overall the predictions of treated patients and the number of injections for RVO were overestimated in the first year of listing, but are now appearing underestimated. The predictions for BRVO appear more underestimated than CRVO.

In Year 1, for BRVO the number of predicted versus actual patients was similar whereas the number of CRVO patients was underestimated (Table 43). By Year 3 of listing, the number of actual patients was greater than predicted for both CRVO and BRVO, particularly for BRVO (Table 43).

The ranibizumab submission estimated incident RVO patients would be 20-30% BRVO and 70-80% CRVO. It estimated response rates of 60.3% and 50.8% for BRVO and CRVO respectively, with 63% and 79% continuing on treatment in year 2. Overall this implies 38.0% of BRVO initiators and 40.1% of CRVO initiators would continue treatment in the second year.

The RVO analysis showed that for BRVO 54% of patients who initiated in 2015 were treated 12-24 months after initiation, and 47% of patients who initiated in 2016 were treated 12-24 months after initiation. For CRVO 53% of patients who initiated in 2015 were treated 12-24 months after initiation, and 47% of patients who initiated in 2016 were treated 12-24 months after initiation. This implies the submission's estimates of continuation were underestimated, which has likely contributed to RVO being incorrectly estimated to be a smaller market than DMO.

In Years 2 and 3, the actual number of injections for BRVO was substantially higher than predicted due to a greater number of treated patients than anticipated (Table 43). The number of injections for CRVO was overestimated in Years 1 and 2 as there were fewer patients treated than projected (Table 43). In Year 3, there were more CRVO patients treated than estimated resulting in the number of predicted versus actual injections being similar (Table 43). The actual number of CRVO injections remained less than estimated because of an overestimate in the continuation on therapy for CRVO.

The ranibizumab submission estimated the number of injections responders and non-responders would receive. Overall these figures estimated approximately 6.65 injections for BRVO and 6.49 injections for CRVO. The actual numbers are lower than predicted, for BRVO 5.10 for patients who initiated in 2015 and 6.22 for patients who initiated in 2016; and for CRVO 5.13 for patients who initiated in 2015 and 5.88 for patients who initiated in 2016. The submission for ranibizumab included a bilateral treatment rate of 5%. Between 98-99% of prescriptions for RVO are supplied with a quantity of one. This suggests the bilateral rate was reasonable but possibly overestimated.

Aflibercept - RVO

[redacted]

Table 44: Predicted number of injections administered per patient of aflibercept for CRVO

[redacted]

Table 45: Predicted number of injections administered per patient of aflibercept for BRVO

[redacted]

Table 46: Aflibercept actual versus predicted utilisation for RVO

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients treated per year					
BRVO					
Predicted		[redacted]	[redacted]	[redacted]	[redacted]
Actual	1,934	4,148	6,211		
Difference		[redacted]	[redacted]		
CRVO					
Predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	1,286	3,099	4,799		
Difference		[redacted]	[redacted]		
Total					
Predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	3,191	7,118	10,781		
Difference	[redacted]	[redacted]	[redacted]		
Total number of injections					
BRVO					
Predicted		[redacted]	[redacted]	[redacted]	[redacted]
Actual	4,817	16,957	27,634		
Difference		[redacted]	[redacted]		
CRVO					
Predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	3,087	12,393	20,406		
Difference		[redacted]	[redacted]		
Total					
Predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	7,904	29,350	48,040		
Difference	[redacted]	[redacted]	[redacted]		

[redacted]

[redacted]

[redacted]

[redacted]

Discussion

In consideration of the 2015 AMD report, DUSC noted that the patterns of use evolved over several years from the time when ranibizumab was listed and considered it too early to assess whether the availability of aflibercept will change patterns of use in Australian clinical practice. The current analysis suggests the use of aflibercept has continued to grow and aflibercept has become the market leader, but has not changed patterns of use.

For AMD, DMO and RVO the number of injections in a patient's first year of treatment are nearly identical for patients solely treated with either ranibizumab or aflibercept, and similar for patients who initiate on one and switch to the other within the year. This is consistent with the PBAC's consideration that the price of aflibercept should be based on an injection: injection basis. It appears that the advice received in response to the 2015 analysis, that clinicians are using a "treat and extend" regimen to treat AMD, is continuing.

Use of medicines for AMD has continued to grow since the 2015 DUSC report. In 2017 50,964 patients were treated for AMD. Of the patients who initiated in 2007, 21% received a treatment for AMD in 2017. As the original estimates for AMD were for five years, it is difficult to determine whether it was predicted that AMD would be treated for more than 10 years in some patients. None of the PBS listings for AMD, DMO or RVO include continuation criteria. It is unclear what benefit patients are getting from treatment after this long, although this analysis is complicated by the possibility of use in the patients second eye years after initiation in the first.

The overall use of ranibizumab and aflibercept did increase following the listings of DMO and RVO, but the majority of use of ranibizumab and aflibercept is for AMD. In 2017 50,964 patients were treated for AMD, 11,137 for DMO (excluding dexamethasone implant), and 10,781 for RVO. The number of patients treated for DMO and RVO appear similar, although the mean number of injections for DMO is higher per patient than for RVO.

This is not consistent with the predicted number of treated patients as it was predicted the number of patients treated for DMO would be approximately twice the number of patients treated for RVO. A comparison of predicted and actual patient numbers suggests this inconsistency is due to both indications, as DMO was overestimated, and RVO was underestimated.

In 2017, 11,137 patients were treated for DMO with VEGF inhibitors. The number of treated patients and the number of injections per patient were overestimated. Patients who initiated in 2016 received an average of 8.72 VEGF inhibitor injections in their first 12

months of treatment. The mean age of patients initiating ranibizumab or aflibercept for DMO was 64.

In 2017, 995 patients were supplied 2,197 dexamethasone implants for DMO. Dexamethasone implant is restricted to use in patients who are unsuitable for, contraindicated to, or who have failed VEGF inhibitors. Of the 995 patients supplied dexamethasone in 2017 approximately half had previously received ranibizumab and/or aflibercept.

Use of medicines for RVO is higher than expected because the number of treated patients and continuation rates were underestimated. The average number of injections per patient is lower than expected. In 2017 10,781 patients were treated for RVO. Since listing, the mean age of patients initiating ranibizumab or aflibercept for RVO was 73 years. Continuation rates and the number of injections per person are similar for BRVO and CRVO.

A high proportion (39 %) of patients commencing PBS subsidised treatment for RVO had previous or subsequent PBS prescriptions for AMD and/or DMO. This was not anticipated. It is possible that there may have been some use of ranibizumab or aflibercept for RVO outside of the restrictions before it was listed.

Consistent with the disease aetiology, the proportion of bilateral treatment is higher for DMO than for AMD, and very low in RVO. For DMO approximately 30% of prescriptions are supplied with a quantity of two indicating bilateral treatment. For AMD approximately 10% of prescriptions are supplied with a quantity of two.

DUSC consideration

DUSC noted the utilisation analysis shows the use of these medicines has continued to grow, and the rate of growth does not appear to be slowing. DUSC commented the growth is predominantly driven by use in AMD, but noted there was an additional increase in the market following the listings for DMO and RVO.

DUSC commented that patient characteristics such as age, the proportion of bilateral treatment, the number of injections per prescription and continuation for each indication are consistent with expectations and the disease aetiology.

DUSC noted there are no continuation criteria in the PBS restrictions for any of the listed indications for patients to access continuing treatment. DUSC commented the time horizon for the original consideration of cost-effectiveness was five years. DUSC noted the report showed approximately 50% of initiating AMD patients were still treated five years after initiation, and one quarter of initiating AMD patients were treated beyond 10 years. DUSC considered ESC or PBAC may wish to consider whether use beyond five years is cost-effective.

DUSC commented that the analysis of the number of injections per patient per year by year of initiation suggested that over time patients are being treated more intensively in their first year of treatment. DUSC considered this is partly driven by switching since aflibercept has listed, as patients who have switched are treated with a second induction phase of the new medicine.

DUSC noted the report showed the use of RVO was underestimated. DUSC commented that the limited data in the report suggested the treatment duration of RVO may be longer than expected, and RVO patients may be treated more frequently than predicted.

DUSC noted the report showed the use of DMO was overestimated. DUSC noted the sponsor of aflibercept and the sponsor of ranibizumab questioned whether the data regarding indication contains pharmacy coding errors. DUSC considered the overestimate of DMO could be partially explained if some patients were treated under the AMD restriction for DMO.

DUSC noted that dexamethasone implant was recommended on the basis of inferior effectiveness and inferior safety compared to ranibizumab and aflibercept. DUSC noted 995 patients were treated with dexamethasone implants in 2017, and these patients used an average number of 2.21 injections per patient, which suggests the average dosage frequency was six months.

DUSC noted the proportion of dexamethasone implant prescriptions dispensed with a quantity of two injections was 17.49% in 2017. DUSC commented that overall, use of dexamethasone is low, but considered there is early evidence that dexamethasone implants may be being used inappropriately. DUSC suggested that because of its inferior effectiveness and inferior safety, the use of dexamethasone should be further monitored.

DUSC noted the response from the sponsor of aflibercept, which included an analysis of a 10% sample of PBS data. DUSC noted the analysis included some analyses replicated from the DUSC report, and some further analyses. DUSC noted the response found the average ages of persons receiving medicines for the three indications were similar to the findings of the DUSC report.

DUSC noted the response stated 25% of patients switched to aflibercept from ranibizumab, and that the response suggested this implicitly implies aflibercept is a more effective treatment. DUSC considered that as the second agent to market, it was expected that more patients will switch to aflibercept rather than from aflibercept.

DUSC noted the analysis of duration presented in the response and noted that the sponsor considered this showed the length of treatment of aflibercept was longer than for ranibizumab. DUSC considered this analysis was affected by a survivor bias, due to the natural attrition from ranibizumab to aflibercept. DUSC noted that the response assumed continuing patients have stable disease, however DUSC considered this cannot be assumed or verified without health outcome data, such as visual acuity scores. DUSC considered duration estimates are not a measure of efficacy and the length of time on treatment can be affected by many things, including perceptions of efficacy or safety or frequency of administration.

DUSC noted the response included a time to refill analysis for aflibercept and ranibizumab, for treatment naïve patients who initiated on or after 1 December 2012, separated by the first three injections per patient and subsequent injections. The response stated that there is evidence of 'treat-and-extend' being used for all indications, particularly for AMD and CRVO. The sponsor noted that the peak at 28 days is most prominent for timing between loading doses, and the bulk of the distribution has moved to longer time between refills for subsequent doses. DUSC commented the use of 'treat-and-extend' protocols has previously been noted, and that the histogram of time to refill was flatter for subsequent injections than the initial three injections for both ranibizumab and aflibercept. DUSC commented the time to refill is also not linked to outcomes data, and considered the differences between the two drugs to be insubstantial.

The utilisation analysis compared the number of injections per patient for patients who initiated in a calendar year, stratified by whether the patient was only treated with aflibercept, only treated with ranibizumab, switched from aflibercept to ranibizumab, or switched from ranibizumab to aflibercept in that year. DUSC noted the report found the number of injections per patient was numerically lower for ranibizumab than aflibercept, and that the report stated these numbers were similar.

DUSC noted the sponsor of aflibercept completed a similar analysis in the 10% sample, with the additional requirement that patients received at least one prescription in the following year. DUSC noted the sponsor stated that patients stopping treatment during the year would naturally receive fewer average treatments than patients who continue treatment. DUSC noted the sponsor's analysis showed the number of injections per patient was numerically lower for aflibercept than ranibizumab, and DUSC considered the number of injections per patient were similar.

DUSC noted the response from the Department of Human Services (DHS) which noted there was a high volume of authority applications received for aflibercept and ranibizumab. DHS considered that there was good prescriber behaviour and understanding of the restriction criteria for both ranibizumab and aflibercept. As such, DHS considered there may no longer be a need to have an authority level of Authority Required - Written for initial authorities and Authority Required - Telephone for continuing authorities. To reduce the administrative burden of these medicines, DHS raised whether it would be appropriate to relax the authority levels to Authority Required - Telephone for initial authorities; Authority Required (STREAMLINED) for the continuing treatment phase and subsequent continuing phase.

DUSC actions

- DUSC requested that the report be provided to the PBAC.
- DUSC requested that the Secretariat and DHS investigate whether pharmacy coding errors have affected the data.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor's comments

Bayer Australia Ltd: Bayer thanks the DUSC for the opportunity to respond to the analysis and for its consideration of our response.

Allergan Australia Pty Limited: The sponsor has no comment.

Novartis Pharmaceuticals Australia Pty Limited: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A

Approach taken to estimate utilisation

AMD

Ranibizumab March 2007 PBAC submission

The submission's estimate of total number of packs of ranibizumab supplied (or prescriptions dispensed) per year assumed that all newly diagnosed eyes received 7 packs in their first year of treatment and continuing eyes received 6 packs in subsequent years, with the exception of the "continuing" cohort in year one. Most of the patients in the continuing cohort in year one were counted as being new to ranibizumab treatment and assumed to receive 7 treatments, other than those who received ranibizumab via the Special Access Scheme, who will receive no more than 6 or 5 treatments in the first year of listing.

The 5-year economic model incorporated the effects of a proposal offering the PBS a refund for all treatments with ranibizumab beyond 15 injections per eye for the initial three years of listing. The PBAC recommended this maximum be set on a per patient basis, because it would be administratively difficult to monitor PBS usage on a per eye basis.

Aflibercept March 2012 PBAC submission

The submission assumed uptake would be higher in incident patients than in patients already being treated with ranibizumab. The submission stated that these estimates assume that the likelihood of newly diagnosed patients being treated with aflibercept rather than ranibizumab will increase over time up to the end of year 3, and that patients who have not switched from ranibizumab to aflibercept by the end of year 2 will be less likely to switch in future years. The submission did not include an estimate of patients receiving bilateral treatment.