

Age Related Macular Degeneration: utilisation analysis

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), including a 24 month predicted versus actual analysis of aflibercept (listed 1 December 2012).

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

- Ranibizumab listed 1 August 2007
- Aflibercept listed 1 December 2012

Data Source / methodology

Data were extracted from the Department of Human Services (DHS) Medicare Pharmacy Claims database for the period August 2007 to December 2014, inclusive.

Key Findings

- In 2014, 36,739 patients received at least one treatment for AMD. A total of 249,772 injections of aflibercept and ranibizumab were supplied through the PBS at a cost to Government of about \$250 million.
- Between 7,000 and 8,000 new patients start treatment for wet AMD each year. The number of new patients is relatively stable.
- 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 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.
- The rate of bilateral treatment appears to be increasing, although there is limited information available to estimate this use.

- 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 appears to be similar. Patients who initiated AMD treatment between December 2012 and November 2013 and were only treated with one agent used an average of 9.30 injections of ranibizumab and 8.28 injections of aflibercept. For continuing patients, those who switched to aflibercept had a higher average number of injections in the next 12 months (8.71) than those who remained on ranibizumab (6.90).
- Utilisation of aflibercept and ranibizumab for wet AMD will continue to increase in to the future due to an ageing population, high rates of continuation on treatment and a high number of injections per patient per year.

Purpose of analysis

To assess the utilisation of PBS listed medicines for age related macular degeneration (AMD), including a 24 month predicted versus actual analysis of aflibercept.

Background

The medicines included in this review are those currently listed on the PBS for the treatment of AMD: verteporfin (listed 1 August 2007), ranibizumab (listed 1 August 2007) and aflibercept (listed 1 December 2012). The use of verteporfin is very low but is included for completeness. The detailed analyses in this report focus on aflibercept and ranibizumab.

Pharmacology

Ranibizumab and aflibercept are antineovascularisation agents, ATC code: S01LA04 and S01LA05 respectively.

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Verteporfin is used as a light-activated drug (photosensitiser). Treatment with verteporfin requires administration of both verteporfin by intravenous infusion and nonthermal red light.

Therapeutic Goods Administration (TGA) approved indications

Table 1: TGA approved indications

| | Ranibizumab | Aflibercept | Verteporfin |
|---|-------------|-------------|----------------|
| Neovascular (wet) age-related macular degeneration | ✓ | ✓ | ✓ ^a |
| Visual impairment due to diabetic macular oedema | ✓ | ✓ | - |
| Visual impairment due to macular oedema secondary to RVO | ✓ | ✓ | - |
| Visual impairment due to CNV secondary to pathologic myopia | ✓ | - | |

^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

Visudyne (verteporfin) Australian approved product information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 1 August 2007, last updated 24 September 2013

Sourced 4 May 2015

Dosage and administration

Table 2: Dosage and administration of ranibizumab, aflibercept and verteporfin for AMD

| Brand name and sponsor | Dose and frequency of administration from Product Information |
|---|---|
| Ranibizumab (Lucentis®), Novartis Pharmaceuticals Australia Pty Limited | 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given as a single intravitreal injection Ranibizumab is given monthly. The interval between two doses should not be shorter than 1 month. Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to a lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly. |
| Aflibercept (Eylea®), Bayer Australia Ltd | The injection volume is 50 µL (equivalent to 2 mg aflibercept). Aflibercept treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. Long term, it is recommended that patients continue to be treated every 2 months. Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes. The dosing interval can be extended up to every three months. ^a The interval between doses injected in the same eye should not be shorter than one month. |
| Verteporfin (Visudyne®), Novartis Pharmaceuticals Australia Pty Limited | 10 minute intravenous infusion of verteporfin at a dose of 6 mg/m ² body surface area, diluted in 30 mL infusion solution, followed by light activation of verteporfin 15 minutes after the start of the infusion. Patients should be re-evaluated every 3 months. In the event of recurrent CNV leakage, verteporfin treatment should be repeated. |

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
Visudyne (verteporfin) Australian approved product information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 1 August 2007, last updated 24 September 2013
Sourced 4 May 2015

^aThe aflibercept Product Information (PI) contains further information regarding dosing and administration as follows: Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. There is limited information on the optimal dosing interval and monitoring interval especially for long term (e.g. > 12 months) treatment. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued.

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 March 2015)

Table 3: PBS listing of verteporfin

| Item | Name, form & strength, pack size | Max. quant. | Rpts | DPMQ | Brand name and manufacturer |
|-------|---|-------------|------|-----------|--|
| 1349B | verteporfin 15 mg injection, 1 x 15 mg vial | 1 | 0 | \$2246.70 | Visudyne Novartis Pharmaceuticals Australia Pty Limited |

Source :<http://www.pbs.gov.au/medicine/item/1349B>

Table 4: PBS listing of ranibizumab

| Item | Name, form & strength, pack size | Max. quant. | Rpts | DPMQ | Brand name and manufacturer |
|--------|--|-------------|------|------------|--|
| 1382R | ranibizumab 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial | 1 | 2 | \$1431.50* | Lucentis Novartis Pharmaceuticals Australia Pty Limited |
| 10138N | ranibizumab 1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe | 1 | 2 | \$1431.50* | |

*special pricing arrangement applies

Source: <http://www.pbs.gov.au/medicine/item/10138N-1382R>

Table 5: PBS listing of aflibercept

| Item | Name, form & strength, pack size | Max. quant. | Rpts | DPMQ | Brand name and manufacturer |
|-------|--|-------------|------|------------|------------------------------|
| 2168D | aflibercept 4 mg/0.1 mL injection, 1 x 0.1 mL vial | 1 | 2 | \$1431.50* | Eylea Bayer Australia Ltd |

*special pricing arrangement applies

Source: <http://www.pbs.gov.au/medicine/item/2168D>

Restriction

Verteporfin is PBS listed as an Authority Required listing as the sole PBS-subsidised therapy, of predominantly (greater than or equal to 50%) classic, subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD), as diagnosed by fluorescein angiography, in a patient with a baseline visual acuity equal to or better than 6/60 (20/200).

Ranibizumab and aflibercept are PBS listed as Authority Required listings for treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD), as diagnosed by fluorescein angiography.

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

- Ranibizumab listed 1 August 2007
- Verteporfin listed 1 August 2007
- Aflibercept listed 1 December 2012

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

Verteporfin

Verteporfin was approved for listing at the November 2005 PBAC meeting. The PBAC recommended listing on a cost-effectiveness basis for patients with AMD featuring predominantly classic lesions.

For further details refer to the [Public Summary Document](#) from the November 2005 PBAC meeting.

Ranibizumab

Ranibizumab was approved for listing at the March 2007 PBAC meeting. The PBAC recommended listing on the PBS for the treatment of subfoveal choroidal neovascularisation (CNV) due to age related macular degeneration on a cost-effectiveness basis against verteporfin with photodynamic therapy in predominantly classic disease, and against placebo in minimally classic or occult disease. At this time the PBAC did not agree to the sponsor's proposed "as needed" (pro re nata, "p.r.n.") dosing regimen.

Listing was recommended at the price proposed in the submission on the basis of an average incremental cost per extra quality adjusted life year (QALY) gained across all lesion types of \$43,771, assuming a patient receives a total of 15 monthly injections of 0.5 mg ranibizumab in a single eye.

For further details refer to the [Public Summary Document](#) from the March 2007 PBAC meeting.

[REDACTED]

[REDACTED]

[REDACTED]

Aflibercept

Aflibercept was recommended for listing at the March 2012 PBAC meeting. Overall, the PBAC considered the submission's claim that 2 mg aflibercept administered every second month following three initial monthly injections is non-inferior in terms of efficacy and safety to 0.5 mg of ranibizumab administered monthly (for maintenance of vision) was reasonable.

The PBAC noted the submission's cost minimisation analysis compares a treatment frequency for ranibizumab of 8.8 injections per year (based on PBS data analysis for 12-month continuers only) with 7 injections per year for aflibercept. The PBAC noted that there is a high degree of uncertainty regarding the number of injections that will be administered in clinical practice for aflibercept. The analysis of utilisation of ranibizumab shows that this market is changing with longer duration of use and more frequent dosing of ranibizumab.

The PBAC noted the DUSC review of ranibizumab also indicated that approximately 20% of patients were receiving bilateral treatment, and considered that the submission's estimate of the number of prescriptions dispensed for aflibercept is likely to be underestimated as it is based on single eye treatment. Therefore, the PBAC considered that the price of aflibercept should be based on an injection: injection basis with ranibizumab and that the number of doses required each year should not be taken into account.

The PBAC noted that there was no clinical evidence presented in the submission for use of aflibercept in patients who have failed or are unable to continue treatment with ranibizumab and therefore recommended that the restriction should limit use to treatment naïve patients.

For further details refer to the [Public Summary Document](#) from the March 2012 PBAC meeting.

Prior to listing, aflibercept made a submission to the August 2012 PBAC special meeting which requested a change to the restriction recommended at the March 2012 PBAC meeting to allow use of aflibercept in patients who have received prior treatment with ranibizumab.

The PBAC considered that the evidence presented in the submission was supportive of the claim that switching from ranibizumab to aflibercept was likely to have similar efficacy and safety as remaining on ranibizumab in patients who had demonstrated a response to treatment with ranibizumab. However, the PBAC noted that the trials presented in the submission did not include patients who had failed to respond or were unable to continue treatment with ranibizumab. The PBAC considered that it was appropriate to limit use of aflibercept in patients switching from ranibizumab to treatment responders, but acknowledged that to write a restriction around this would require inclusion of continuation rules which would be complex and difficult to administer. The PBAC also noted that the restriction for ranibizumab does not require patients to demonstrate a response in order to access continuing treatment. The PBAC considered that the invasive

nature of treatment would likely limit use of anti-VEGF treatments in patients who are not achieving a clinical benefit.

Approach taken to estimate utilisation

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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.

Methods

Prescription data were extracted from the Department of Human Services (DHS) Medicare Pharmacy Claims database for the period August 2007 to December 2014, inclusive.

The number of prescriptions is presented for aflibercept, ranibizumab and verteporfin. As verteporfin use is very low, the number of patients and prescription per patient analyses are conducted for aflibercept and ranibizumab only.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of

processing data.¹ The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included. The DHS Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

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.

Novartis ran an access program before the listing of ranibizumab on the PBS on 1 August 2007. 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.

Number of injections per patient

The number of treatments per patient per year was examined using deidentified individual patient data. The cohorts comprised patients who were supplied an initial prescription for an AMD medicine (either ranibizumab or aflibercept) 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 2014. The follow-up period varies from one year for those who initiated treatment in 2013, to seven years for those who initiated in 2007. For patients initiating in 2014 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 and median for each available 12 month period for each cohort.

To assess the patterns of use once aflibercept became available, the analysis of the cohort of patients who initiated in the first year listing year (1 December 2012 to 30 November 2013) are further examined by their initiating and subsequent drugs.

Analyses were undertaken in SAS.

¹ Australian Government Department of Human Services Medicare. PBS statistics. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Overall utilisation

Figure 1 and Table 6 show the number of patients starting treatment with PBS subsidised aflibercept or ranibizumab for the first time (initiating), and the total number of patients receiving treatment with aflibercept or ranibizumab (prevalent).

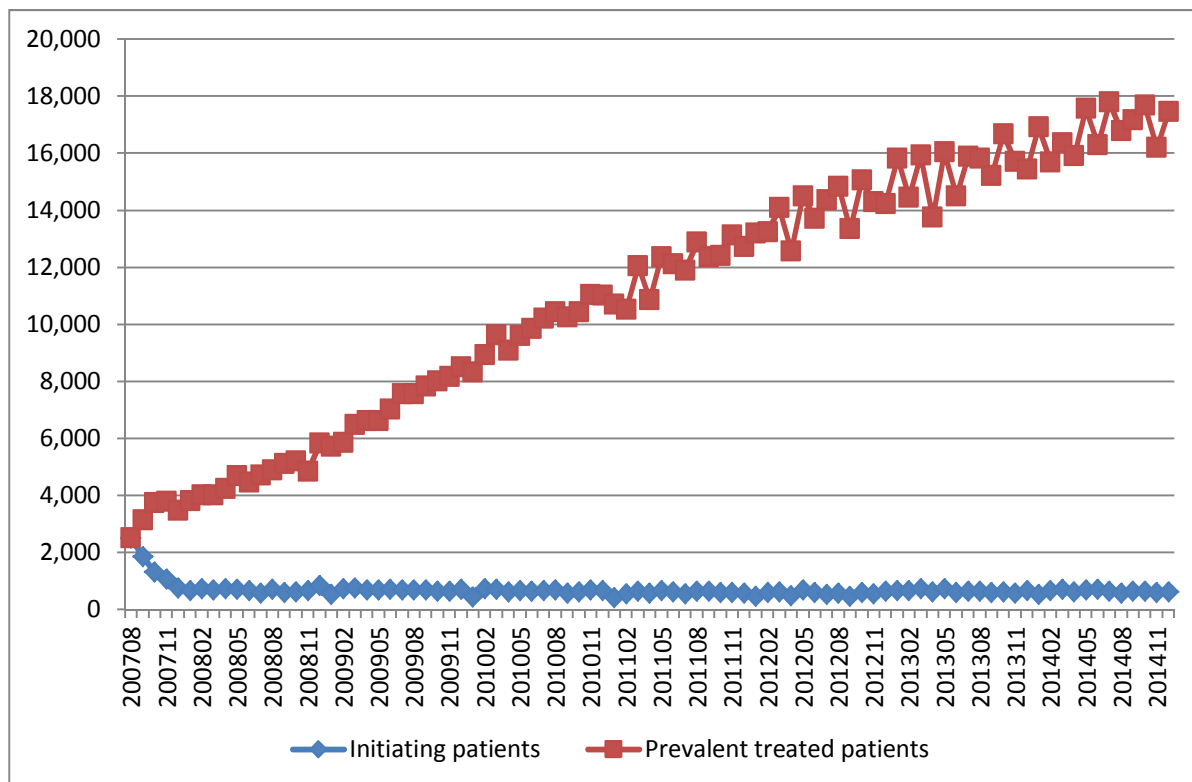


Figure 1: Number of initial patients and all patients treated each month from August 2007 to December 2014

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

The number of patients initiating treatment is stable while the number of prevalent treated patients continues to grow.

Figure 2 shows the number of injections (solid line) and number of prescriptions (broken line) for medicines used to treat AMD. The usual maximum quantity per prescription is one injection of either aflibercept or ranibizumab, but some prescriptions are authorised for an increased maximum quantity.

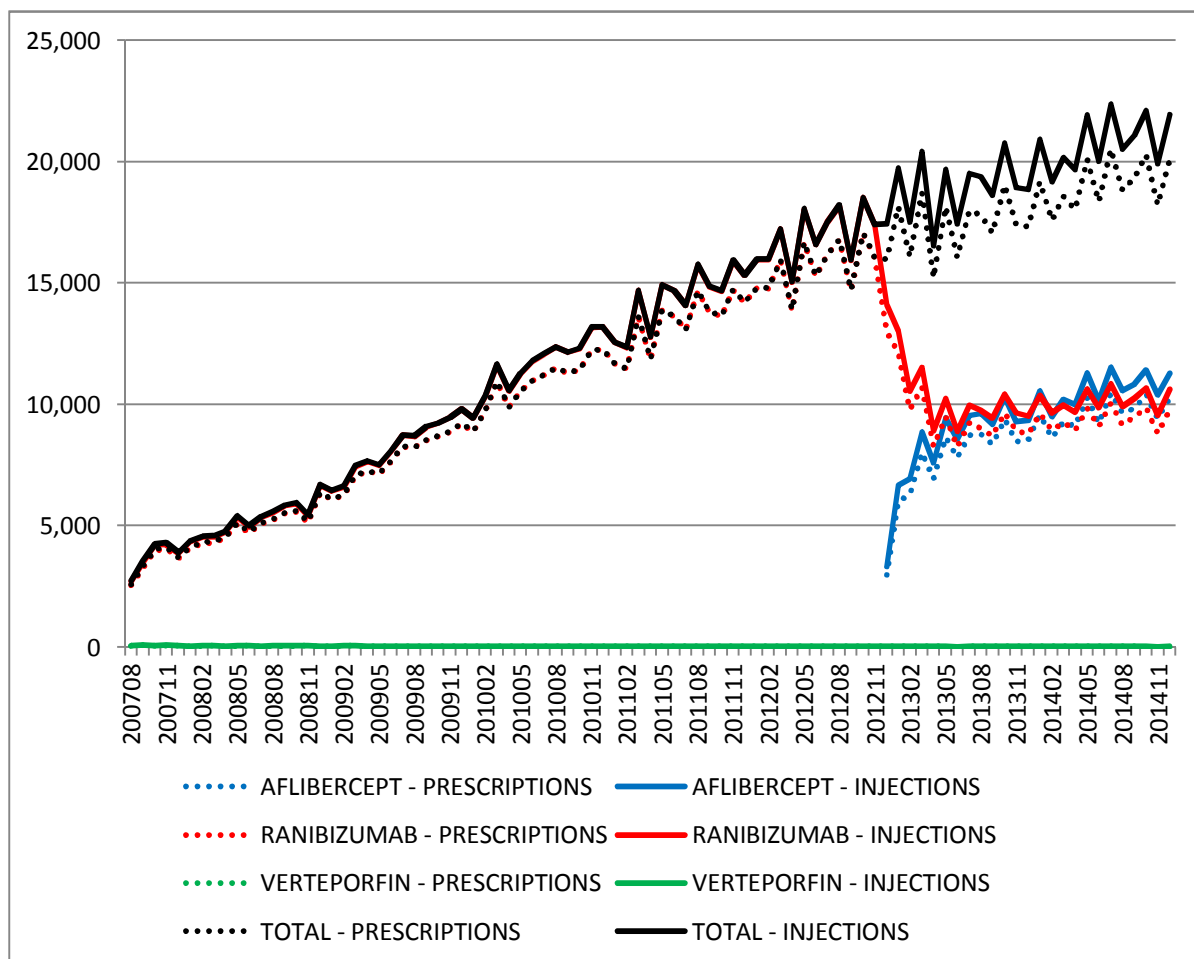


Figure 2: Prescriptions and supplied injections for ranibizumab, aflibercept and verteporfin, from August 2007 to December 2014

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

The total number of prescriptions has increased steadily over the past eight years. There is a small but increasing divergence between the number of injections and prescriptions over time.

Uptake of aflibercept following listing on 1 December 2012 was rapid, reaching 50% market share within 6 months. The addition of aflibercept to the PBS does not appear to have increased the growth of the market beyond the previous trend. Aflibercept is being used in both new patients and for patients switching from ranibizumab (see pages 21-25).

The use of verteporfin is low with only 132 prescriptions supplied in 2014. Another AMD medicine, anecortave, was listed on the PBS between 1 April 2007 and 30 June 2009. Its use was lower than verteporfin and is not presented in Figure 2. Both verteporfin and anecortave are excluded from further analyses in this report.

The annual number of patients, prescriptions and injections is summarised in Table 6.

Table 6: Summary of patients accessing AMD treatment and number of supplied prescriptions, supplied injections and injections per patient by calendar year

| | New patients | Prevalent patients | Prescriptions supplied | Injections supplied | Calculated injections per prevalent patient |
|------|--------------|--------------------|------------------------|---------------------|---|
| 2007 | 7,478 | 7,478 | 17,482 | 18,492 | 2.47 |
| 2008 | 8,205 | 14,320 | 59,786 | 63,177 | 4.41 |
| 2009 | 8,125 | 18,889 | 93,087 | 98,612 | 5.22 |
| 2010 | 7,654 | 22,834 | 130,814 | 140,245 | 6.14 |
| 2011 | 7,097 | 26,132 | 160,194 | 172,548 | 6.60 |
| 2012 | 6,874 | 29,269 | 188,027 | 203,751 | 6.96 |
| 2013 | 7,765 | 33,347 | 208,919 | 227,193 | 6.81 |
| 2014 | 7,622 | 36,739 | 229,083 | 249,772 | 6.80 |

The figure for 2007 represents the first five months of listing

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

Over 60,000 patients have been treated since 2007. Approximately 7,600 new patients start treatment each year. This number has been reasonably stable, except in 2012 where the number of new patients was lower than in other years. Aflibercept was PBS listed at the end of this year.

In 2014, 36,739 patients were treated with aflibercept and/or ranibizumab. The total number of people on treatment has been increasing each year, although the rate of growth appears to be slowing to a small extent. For example, when compared to the previous year, growth in 2011 was 14% and in 2014 was 10%.

The total numbers of prescriptions and injections have also increased over time. The calculated number of injections per prevalent patient increased progressively until 2011, and has been fairly constant since then (~6.8 injections/patient/year). The 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. An analysis of the prescription histories of individual deidentified patients, presented on pages 15-16, provides further insight into how the number of injections per patient has evolved over time.

Table 7 shows that the proportion of supplied prescriptions where an increased maximum quantity of two injections was authorised has increased slowly over time.

Table 7: Proportion of prescriptions by quantity dispensed over time

| | 1 | 2 | 3 | 6 |
|------|----------|----------|----------|----------|
| 2007 | 94.26% | 5.74% | 0.00% | 0.00% |
| 2008 | 94.32% | 5.64% | 0.04% | 0.00% |
| 2009 | 94.06% | 5.92% | 0.02% | 0.00% |
| 2010 | 92.79% | 7.20% | 0.01% | 0.00% |
| 2011 | 92.29% | 7.71% | 0.00% | 0.00% |
| 2012 | 91.64% | 8.36% | 0.00% | 0.00% |
| 2013 | 91.22% | 8.74% | 0.03% | 0.00% |
| 2014 | 90.91% | 9.03% | 0.06% | 0.00% |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

A quantity of two suggests the injections were for an increased maximum quantity, perhaps to treat both eyes at once or close together. A quantity of three or six suggests these patients were dispensed all of the repeats at once, under regulation 24. Further discussion on the rates of bilateral treatment is provided in a later section.

Injections per patient and continuation rates

The main uncertainties at the time of listing ranibizumab and aflibercept included the number of injections per patient per year, continuation rates and duration of treatment. A utilisation analysis in cohorts of patients initiating AMD treatment in each calendar year was undertaken to examine these factors. The analysis does not distinguish by the drug prescribed because the PBAC recommended aflibercept on an injection : injection basis with ranibizumab. However, the predicted versus actual assessment of aflibercept presented later in this report compares the number of injections of aflibercept and ranibizumab (pages 23-25).

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.

The number of patients who initiated in 2014 is known, but there is insufficient data available to assess how many injections they received in their first full twelve months.

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 |
|----------------|--------|--------|--------|--------|--------|--------|--------|
| Initiated 2007 | 7,478 | 4,853 | 4,273 | 3,883 | 3,577 | 3,265 | 2,938 |
| Initiated 2008 | 8,205 | 5,078 | 4,302 | 3,905 | 3,534 | 3,223 | |
| Initiated 2009 | 8,125 | 5,377 | 4,608 | 4,153 | 3,757 | | |
| Initiated 2010 | 7,654 | 5,362 | 4,630 | 4,116 | | | |
| Initiated 2011 | 7,097 | 5,206 | 4,544 | | | | |
| Initiated 2012 | 6,874 | 5,165 | | | | | |
| Initiated 2013 | 7,765 | | | | | | |
| Initiated 2014 | 7,623 | | | | | | |

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 |
|----------------|--------|--------|--------|--------|--------|--------|--------|
| Initiated 2007 | 100% | 65% | 57% | 52% | 48% | 44% | 39% |
| Initiated 2008 | 100% | 62% | 52% | 48% | 43% | 39% | |
| Initiated 2009 | 100% | 66% | 57% | 51% | 46% | | |
| Initiated 2010 | 100% | 70% | 60% | 54% | | | |
| Initiated 2011 | 100% | 73% | 64% | | | | |
| Initiated 2012 | 100% | 75% | | | | | |
| Initiated 2013 | 100% | | | | | | |

The majority of patients continue into the second year of treatment. There is a trend of increasing rates of continuation into the second year over time (65% in 2007 up to 75% in 2012). Continuation rates in subsequent years remain high. 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. The 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.

The DUSC considered that discontinuation rates have been lower than anticipated, and duration of use longer than anticipated contributing to the growth in the number of prevalent patients treated. The 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 tables below display the mean and median number of injections of ranibizumab and aflibercept patients receive in each year of treatment, by the calendar year of initiation.

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 |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|
| Initiated 2007 ^a | 5.70 | 5.95 | 7.19 | 7.67 | 7.96 | 7.88 | 7.66 |
| Initiated 2008 | 6.11 | 6.12 | 6.98 | 7.37 | 7.62 | 7.38 | - |
| Initiated 2009 | 7.23 | 6.78 | 7.30 | 7.51 | 7.27 | - | - |
| Initiated 2010 | 8.08 | 7.20 | 7.43 | 7.47 | - | - | - |
| Initiated 2011 | 8.31 | 7.20 | 7.10 | - | - | - | - |
| Initiated 2012 | 8.48 | 7.04 | - | - | - | - | - |
| Initiated 2013 | 8.29 | - | - | - | - | - | - |

Source: DHS Medicare Pharmacy Claims database, accessed March 2015

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

Table 10: The median 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 |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|
| Initiated 2007 ^a | 5 | 5 | 6 | 7 | 7 | 7 | 7 |
| Initiated 2008 | 6 | 5 | 6 | 6 | 7 | 6 | - |
| Initiated 2009 | 7 | 6 | 6 | 7 | 6 | - | - |
| Initiated 2010 | 8 | 6 | 7 | 6 | - | - | - |
| Initiated 2011 | 8 | 7 | 6 | - | - | - | - |
| Initiated 2012 | 8 | 6 | - | - | - | - | - |
| Initiated 2013 | 8 | - | - | - | - | - | - |

Source: DHS Medicare Pharmacy Claims database, accessed March 2015

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

The 2012 analysis of AMD investigated the average number of prescriptions supplied in the first 12 months of therapy, and reported that the number of prescriptions filled per cohort was steadily increasing each year. Tables 9 to 10 show the number of injections supplied in the first 12 months of therapy now appears to be stable at around 8 injections per year. Each cohort demonstrates a higher number of injections supplied in the first year of treatment, compared with subsequent years, probably reflecting the more frequent dosing schedule in the first few months of treatment.

Of the 60,821 patients who had been supplied ranibizumab or aflibercept through the PBS up until the end of December 2014, 25,825 (42%) have had more than 15 injections, and 12,763 (21%) have had more than 30 injections. It is not known what proportion of these injections have been to treat the same eye. The ranibizumab submission estimated bilateral treatment in 10% of patients, and data from DHS provided in the 2012 DUSC report indicated about 20%. The proportion of use for bilateral treatment is discussed further below.

Table 11: Number and percentage of patients who have had more than 15 and 30 injections, by year of initiation

| | 15 injections | | 30 injections | |
|-----------------------|--|----------------------------------|--|----------------------------------|
| | Number of patients (%) less than or equal to | Number of patients (%) more than | Number of patients (%) less than or equal to | Number of patients (%) more than |
| Initiated 2007 | 3,441 (46%) | 4,037 (54%) | 4,671 (62%) | 2,807 (38%) |
| Initiated 2008 | 4,103 (50%) | 4,102 (50%) | 5,526 (67%) | 2,679 (33%) |
| Initiated 2009 | 3,680 (45%) | 4,445 (55%) | 5,417 (67%) | 2,708 (33%) |
| Initiated 2010 | 3,285 (43%) | 4,369 (57%) | 5,269 (69%) | 2,385 (31%) |
| Initiated 2011 | 3,013 (42%) | 4,084 (58%) | 5,598 (79%) | 1,499 (21%) |
| Initiated 2012 | 3,585 (52%) | 3,289 (48%) | 6,284 (91%) | 590 (9%) |
| Initiated 2013 | 6,358 (82%) | 1,407 (18%) | 7,670 (99%) | 95 (1%) |
| Initiated 2014 | 7,531 (99%) | 92 (1%) | 7,623 (100%) | 0 |

Source: DHS Medicare Pharmacy Claims database, accessed March 2015

Between 1 August 2007 and 31 December 2014 a total of 548,145 injections have been supplied for 16th or subsequent treatments. The number of injections for 31st or subsequent treatment is 262,716 injections.

Proportion of use for bilateral treatment

Table 7 showed that the proportion of supplied injections where an increased maximum quantity was authorised was increasing 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, either 2, 3 or 6 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 prescriptions with an increased maximum quantity, in each year of treatment, by the calendar year of initiation

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-----------------------|----|----|-----|-----|-----|-----|-----|
| Initiated 2007 | 6% | 8% | 10% | 11% | 11% | 11% | 11% |
| Initiated 2008 | 5% | 7% | 9% | 10% | 12% | 13% | - |
| Initiated 2009 | 5% | 7% | 9% | 10% | 10% | - | - |
| Initiated 2010 | 6% | 8% | 10% | 12% | - | - | - |
| Initiated 2011 | 5% | 7% | 10% | - | - | - | - |
| Initiated 2012 | 5% | 7% | - | - | - | - | - |
| Initiated 2013 | 5% | - | - | - | - | - | - |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

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.

The February 2012 ranibizumab utilisation analysis included authority approval data for August 2010. It estimated approximately 20% of use is for bilateral treatment; 10.5% were for both eyes at different times, and 11.1% for both eyes simultaneously. Tables 7 and 12 suggest the proportion of patients receiving bilateral treatment is increasing over time.

The 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. The 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. The 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.

Age and state/territory of treated patients

Table 13 shows the average age of new patients starting treatment with ranibizumab or aflibercept.

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

| | Mean (range) |
|----------------|------------------|
| Initiated 2007 | 80 (40 - 102) |
| Initiated 2008 | 80 (25 - 102) |
| Initiated 2009 | 80 (41 - 102) |
| Initiated 2010 | 80 (34 - 102) |
| Initiated 2011 | 80 (28 - 102) |
| Initiated 2012 | 80 (33 - 102) |
| Initiated 2013 | 80 (7 - 103) |
| Initiated 2014 | 80 (23 - 101) |

There were 75 patients excluded from this analysis as their age was missing on their first prescription.
Source: DHS Medicare Pharmacy Claims database, accessed April 2015

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. This is similar to average initiation age of PBS patients of 80 years.

Table 14 shows the number of people treated in each state/territory.

Table 14: Geographical state of patients receiving ranibizumab and aflibercept by year of treatment

| Year | ACT | NSW | NT | QLD | SA | TAS | VIC | WA | Un-known | Total |
|------|-----|--------|----|-------|-------|-------|-------|-------|----------|--------|
| 2007 | 156 | 3,234 | | 1,277 | 450 | 269 | 1,655 | 431 | 6 | 7,478 |
| 2008 | 270 | 6,005 | 10 | 2,702 | 912 | 472 | 2,987 | 953 | 9 | 14,320 |
| 2009 | 351 | 7,759 | 19 | 3,557 | 1,374 | 591 | 3,853 | 1,375 | 10 | 18,889 |
| 2010 | 414 | 9,520 | 27 | 4,190 | 1,670 | 657 | 4,650 | 1,696 | 10 | 22,834 |
| 2011 | 497 | 10,909 | 36 | 4,837 | 1,887 | 792 | 5,097 | 2,066 | 11 | 26,132 |
| 2012 | 599 | 12,162 | 43 | 5,483 | 2,002 | 911 | 5,692 | 2,366 | 11 | 29,269 |
| 2013 | 693 | 13,769 | 45 | 6,236 | 2,363 | 1,008 | 6,569 | 2,655 | 9 | 33,347 |
| 2014 | 807 | 15,139 | 47 | 6,761 | 2,648 | 1,090 | 7,323 | 2,915 | 9 | 36,739 |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

As not every state has the same distribution of ages, and AMD becomes more prevalent with increasing age, the following table standardises the number of people treated by the size of the population aged over 65.

Table 15: Geographical state of patients receiving ranibizumab and aflibercept by year of treatment standardised by 100,000 population aged 65 or more of state

| Year | ACT | NSW | NT | QLD | SA | TAS | VIC | WA |
|------|-------|-------|-----|-------|-----|-------|-----|-----|
| 2007 | 347 | 278 | | 194 | 156 | 294 | 191 | 132 |
| 2008 | 601 | 516 | 62 | 410 | 317 | 516 | 345 | 291 |
| 2009 | 781 | 667 | 119 | 539 | 478 | 646 | 445 | 420 |
| 2010 | 921 | 819 | 169 | 635 | 581 | 718 | 538 | 518 |
| 2011 | 1,105 | 938 | 225 | 733 | 656 | 866 | 589 | 631 |
| 2012 | 1,332 | 1,046 | 269 | 831 | 696 | 996 | 658 | 723 |
| 2013 | 1,541 | 1,184 | 281 | 945 | 821 | 1,102 | 759 | 811 |
| 2014 | 1,795 | 1,302 | 294 | 1,025 | 921 | 1,192 | 846 | 890 |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

Patients with an 'unknown' state are excluded

Source: Estimated resident population, by sex and age groups—States and territories—at 30 June 2014, ABS 31010DO001_201409 Australian Demographic Statistics, Sep 2014, Table 6,

<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202014?OpenDocument>

There are differences in treatment rates across Australia. Rates of treatment are very low in the Northern Territory and highest in the ACT, NSW and Tasmania. 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 16: Number of injections per patient by geographical state

| Year | ACT | NSW | NT | QLD | SA | TAS | VIC | WA |
|------|------|------|------|------|------|------|------|------|
| 2007 | 2.63 | 2.66 | | 2.32 | 2.42 | 2.42 | 2.18 | 2.67 |
| 2008 | 5.18 | 5.06 | 3.40 | 3.75 | 3.97 | 4.25 | 3.77 | 4.54 |
| 2009 | 5.91 | 5.87 | 2.68 | 4.37 | 4.96 | 5.72 | 4.65 | 5.28 |
| 2010 | 6.80 | 6.71 | 4.70 | 5.60 | 5.89 | 6.79 | 5.48 | 5.97 |
| 2011 | 6.92 | 7.24 | 4.25 | 6.18 | 6.69 | 6.93 | 5.67 | 6.31 |
| 2012 | 6.98 | 7.71 | 5.56 | 6.46 | 7.17 | 7.82 | 5.84 | 6.50 |
| 2013 | 6.68 | 7.44 | 5.80 | 6.49 | 6.82 | 7.57 | 5.80 | 6.62 |
| 2014 | 6.72 | 7.30 | 6.68 | 6.50 | 6.84 | 7.54 | 6.05 | 6.51 |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

Patients with an 'unknown' state are excluded

Possible reasons for the different rates of treatment could include access to ophthalmologists, remoteness and awareness of the disease and its symptoms. Overall, these tables 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.

Analysis of expenditure

Table 17: PBS benefits for aflibercept and ranibizumab

| | Aflibercept | Ranibizumab | Total |
|--------------------|----------------------|------------------------|------------------------|
| 2007 | | \$35,849,734 | \$35,849,734 |
| 2008 | | \$123,364,942 | \$123,364,942 |
| 2009 | | \$194,130,068 | \$194,130,068 |
| 2010 | | \$276,229,289 | \$276,229,289 |
| 2011 | | \$340,159,478 | \$340,159,478 |
| 2012 | \$6,520,989 | \$395,044,070 | \$401,565,059 |
| 2013 | \$162,235,818 | \$192,669,235 | \$354,905,053 |
| 2014 | \$181,632,805 | \$173,690,065 | \$355,322,870 |
| Grand Total | \$350,389,612 | \$1,731,136,882 | \$2,081,526,494 |

Source: DHS Medicare Pharmacy Claims database using date of supply, which may be slightly different to publicly available Medicare Australia date of processing data, accessed April 2015

The expenditure shown is based on the price published in the PBS schedule. A special pricing arrangement applies to aflibercept and ranibizumab and the published price of aflibercept and ranibizumab was lowered from \$1,976.46 to \$1,431.26 on 1 April 2013.

The DUSC considered it important to note that Commonwealth expenditure presented in this report only relates to PBS expenditure. There are significant additional costs involved in treatment of wet AMD including MBS injection fees.

Analysis of actual versus predicted utilisation

This section of the report compares the predicted and actual utilisation of aflibercept in the first 2 years of PBS listing (1 December 2012 to 30 November 2014).

Two key uncertainties identified at the time of listing are examined:

- the extent of uptake in new and continuing patients
- the number of injections per patient

Uptake of aflibercept

The uptake of aflibercept in newly diagnosed patients was predicted to be █████ in Year 1 and █████ in Year 2. For existing patients treated with ranibizumab, █████ of patients were predicted to switch to aflibercept in Year 1 and █████ in Year 2 of listing.

Table 18 shows the number of patients commencing treatment for AMD in the first two years following PBS listing of aflibercept.

Table 18: New (incident)^a patients treated with aflibercept or ranibizumab

| | Year 1 Dec 12 –Nov 13 | Year 2 Dec 13 –Nov 14 |
|--------------------|--------------------------|--------------------------|
| Aflibercept | 4,277 | 3,457 |
| Ranibizumab | 3,469 | 4,214 |
| Total new patients | 7,746 | 7,671 |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

^adefined as those who have never had a PBS prescription for aflibercept or ranibizumab.

Of the 7,746 patients who initiated AMD treatment in Year 1, 55% initiated on aflibercept and 45% initiated on ranibizumab. In Year 2, the market share in new patients reversed, with 45% of patients starting on aflibercept and 55% on ranibizumab. Uptake of aflibercept in new patients has been higher than expected.

The data in Table 18 above shows the first prescribed medicine. Of the 4,277 patients who initiated treatment with aflibercept in Year 1 of listing, 4,066 (95%) used only aflibercept in the next 12 months, with 211 (5%) switching to ranibizumab. A small number of these, 45, switched more than once. Of the 3,469 patients who initiated treatment with ranibizumab 2,757 patients (79%) only used ranibizumab in the next 12 months, 712 (21%) switched to aflibercept, including 85 who switched more than once.

To determine the proportion of continuing patients who switched to aflibercept, a cohort of patients supplied ranibizumab in the 12 months prior to aflibercept listing (1 December 2011 to 30 November 2012), was identified.

As shown in Table 19, 28,899 patients were treated with ranibizumab in the year prior to aflibercept listing, and 24,265 received at least one prescription of either drug in the following year.

Table 19: Patterns of use of aflibercept in patients previously treated with ranibizumab

| | | |
|--|--------|--------------|
| AMD patients treated with ranibizumab in year prior to aflibercept listing (Dec 11-Nov 12) | 28,899 | |
| AMD patients treated with ranibizumab in year prior to aflibercept listing with at least one prescription of either drug in the following year (Dec 12-Nov 13) | 24,265 | |
| Number (%) of these in the year on: | | |
| ranibizumab only | | 13,489 (56%) |
| aflibercept only | | 3,499 (14%) |
| ranibizumab and switched to aflibercept part way through year | | 5,860 (24%) |
| aflibercept and switched back to ranibizumab part way through year | | 1,417 (6%) |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

About half (56%) of existing patients continuing on treatment into the first year that aflibercept was available remained on ranibizumab. The remaining patients (44%) received at least one aflibercept prescription in the first year that it was available. Although regard is not given to the time during the year that patients switched to aflibercept, the overall finding of this analysis is that the uptake of aflibercept in existing patients has been much higher than expected.

The analyses demonstrate that patients move between the two PBS subsidised treatment options in either direction. The reasons for switching cannot be ascertained from the prescription claim data but may include physician or patient preference, or failure to respond.

Number of injections per patient

For the cost-minimisation analysis, the submission for aflibercept compared a treatment frequency of ranibizumab of 8.8 injections per year (based on PBS data for 12 month continuers only) with 7 injections per year for aflibercept.

In forecasting utilisation, the submission estimated in the first year of listing [redacted] of patients would be continuers and [redacted] would be discontinuers, and that continuers would use [redacted] injections of aflibercept per year and discontinuers [redacted] injections of aflibercept per year. The submission estimated ranibizumab continuers would use [redacted] injections per year and discontinuers [redacted] injections per year. Overall this equates to ranibizumab patients using [redacted] injections per year and aflibercept patients [redacted] injections per year.

In recommending aflibercept for listing, the PBAC noted that there is a high degree of uncertainty regarding the number of injections that will be administered in clinical practice for aflibercept. The PBAC considered that the price of aflibercept should be based on an injection: injection basis with ranibizumab and that the number of doses required should not be taken into account.

The number of injections per patient in their first year of AMD treatment is presented in Table 20. These are patients who received their first ever AMD prescription during the first year of the listing of aflibercept. Their prescription histories are followed for a full 12 months from this first prescription.

Table 20: Number of injections per patient in their first year of AMD treatment

| Medicines received in first 12 months of treatment | Number of patients new to AMD treatment (Dec 12- Nov 13) | Mean number of injections per new patient in their first 12 months of treatment | Weighted mean number of injections per new patient in their first 12 months of treatment by initiating drug |
|--|--|---|---|
| Aflibercept only | 4,066 | 8.28 | 8.13 |
| Aflibercept → ranibizumab | 211 | 5.14 | |
| Ranibizumab only | 2,757 | 9.30 | 8.47 |
| Ranibizumab → aflibercept | 712 | 5.25 | |
| Total incident AMD | 7,746 | 8.28 | |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

The average number of injections in the first year for new patients that were treated with only aflibercept (8.28) was numerically lower than for new patients treated with only

ranibizumab (9.30).

2007 and 2012 ranibizumab submissions

(7 injections).

Of note in this analysis is that the 12% of new patients who switched between aflibercept and ranibizumab or vice versa, had fewer injections (5.14/5.25) than patients remaining on the same treatment. A possible reason for this is that patients who are not responding to one drug may switch to the alternate and also not respond to this and cease therapy. The PBAC, when recommending that patients could switch between aflibercept and ranibizumab (August 2012), had considered that the invasive nature of treatment would likely limit use of anti-VEGF treatments in patients who are not achieving a clinical benefit.

The annual number of injections per patient for those who were on ranibizumab prior to the listing of aflibercept and who continued AMD treatment into the first year of the PBS listing of aflibercept is presented in Table 21.

Table 21: Annual number of injections per patient- ranibizumab to aflibercept

| Medicines received in first 12 months of aflibercept availability | Number of continuing patients in the period (Dec 12- Nov 13) | Mean number of injections per patient in their subsequent 12 months of treatment |
|---|--|--|
| Aflibercept only | 3,483 | 8.71 |
| Ranibizumab only | 13,337 | 6.90 |
| Further ranibizumab then switched to aflibercept | 5,969 | 9.29 |
| Switched to aflibercept and switch back | 1,476 | 12.80 |

Source: DHS Medicare Pharmacy Claims database, accessed April 2015

The overall finding of the analysis of continuing patients is that the number of injections per year has generally been higher than expected (~ 6 injections per year).

The group of continuing patients, whose next injection after aflibercept became available was a switch to aflibercept, had more injections on average in their following 12 months (8.71) compared with patients who remained on ranibizumab (6.90). Patients who had one or more further prescriptions of ranibizumab and then switched to aflibercept had 9.29 injections. One reason the average number of injections for ranibizumab may be lower is that this group includes more patients who died, however this factor cannot be assessed from the available data. As the aflibercept submission had proposed that patients treated with aflibercept would require fewer injections than ranibizumab it is also possible that the group who switched to aflibercept includes a higher proportion undergoing bilateral treatment because of injection burden.

The PBAC recommended aflibercept on an injection : injection basis with ranibizumab. The analysis of injections per patient in the naïve treatment group shows a numerically lower number of injections per patient for aflibercept (8.28) compared with ranibizumab (9.30).

However the reverse is true in continuing patients (8.71 vs 6.90). A longer period of data would be needed to further understand whether there are any significant differences between patterns of use of these agents in practice.

Discussion

The number of people treated with PBS listed agents for wet AMD has doubled over the past 5 years. In 2014, 36,739 patients were treated, and 249,772 injections of aflibercept or ranibizumab were dispensed at a cost to Government of about **\$250 million**. As the likelihood of developing AMD is strongly related to advancing age, and as Australia has an ageing population, it is expected that the prevalent treated group of patients will continue to grow.

Published data from the Blue Mountains Eye Study (BMES) has been used to estimate the incidence and prevalence of patients with AMD in Australia. The BMES estimated the overall 5-year incidence of advanced age-related macular degeneration to be 1.1%; increasing from 0% in individuals under 60 years of age to 5.4% in those aged 80 years or older. Wang et al. (2007) assessed the 10-year incidence of age-related maculopathy (ARM) in an older cohort from the BMES². Comparing across age groups, which were categorised based on the age at base-line, they reported a higher incidence of AMD than from the previously published data. The incidence of AMD rose from 0.17% in the less than 60 years group to 24.3% for the 80 years and older group. Overall, 3.7% of participants (aged ≥49 years) developed late ARM over the ten year period.

Prevalence estimates are also available from two large international studies—the Beaver Dam Eye Study and the Rotterdam Study. Data pooled from these studies and the BMES have estimated the prevalence of advanced age-related macular degeneration to be 0.2% in those aged 55–64 years, increasing to 13% in those older than 85 years.³ The prevalence assumptions used in the original submission for ranibizumab, based on the BMES (Mitchell et al., 1995⁴), were similar to the results of the pooled analysis (0.2% for 55-64 years and 18.5% for the over 85 years group).

In addition to the growing number of people being treated, the numbers of injections dispensed per patient and continuation rates have also increased. The average number of injections that a patient receives in their first year of treatment has increased from 7.2 in 2009 to 8.2 in 2013. Over a similar period of time the proportion of people who remain on treatment into the second year has increased from approximately 65% to 75%. The reasons for this are unknown but could be due to earlier diagnosis or earlier treatment, or changing treatment protocols in clinical practice. The majority of patients remain on treatment for many years. Approximately half of patients are treated for at least 4 years, with 40% of patients still treated 6-7 years after initiation.

² Wang, J.J., Rochtchina, E., Lee, A.J. et al. (2007) Ten-year incidence and progression of age-related maculopathy. *Ophthalmology* 114: 92-98.

³ Hanna R Coleman, Chi-Chao Chan, Frederick L Ferris III, Emily Y Chew (2008) Age-related macular degeneration, *Lancet* 2008; 372: 1835–45

⁴ Mitchell, P., Smith, W., Attebo, K. and Wang, J.J. (1995) Prevalence of age-related maculopathy in Australia. *Ophthalmology* 102: 1450-1460.

The recommendation to list ranibizumab on the PBS was based on an economic model with a time horizon of 5 years⁵. The submission stated, “This time horizon was chosen since the incremental cost-effectiveness ratio did not vary substantially beyond this time point, and the average life expectancy of the patient population is expected to be short; the mean age of the patient population who would receive treatment under the requested PBS indication is expected to be 77 to 78 years based on the clinical trial data. Modelling beyond a time horizon of 5 years would be associated with greater levels of uncertainty in estimating long term benefits, whilst also recognising uncertainty concerning long term ranibizumab treatment use.”

A likely factor contributing to the long time on treatment is use of aflibercept in the second eye. In the key ranibizumab clinical trials (ANCHOR, MARINA and PIER) treatment was restricted to one eye, although the submission’s utilisation estimates assumed a proportion of patients would require treatment in both eyes, either at the same time, or at a later time as a result of developing CNV in their second eye. In the key aflibercept studies (VIEW-1 and VIEW-2) treatment was restricted to one eye and the submission’s utilisation estimates did not account for bilateral treatment.

The PBS data presented in this report do not distinguish treatment in the first eye, second eye, or both eyes. Based on authority approval data presented in the February 2012 DUSC report of ranibizumab, the PBAC (March 2012) considered the extent of use in the second eye per patient could be as high as 20%. The BMES suggested the 10-year incidence of late ARM in the second (fellow) eye of participants with unilateral late ARM at baseline was substantially higher than the incidence in the first eye,² reporting that of the 9 participants with unilateral late ARM at baseline, 5 (55.6%) developed late ARM in their second eye within the first 5 years. Of the 6 participants observed over a 10-year period, 6 of 6 (100%) developed bilateral late ARM within 10 years. The 2-year cumulative incidence of AMD in the fellow eye in subjects with unilateral AMD was found to be 29% in the Rotterdam study,⁶ and the Beaver Dam Eye Study found a 5-year incidence of 22% for the second eye,⁷ considerably lower than the Rotterdam Study. This suggests that between 20-55% of patients diagnosed with AMD will develop bilateral AMD within five years.

An analysis of the prescription processing data shows that the proportion of prescriptions supplied with a quantity of more than one injection is increasing; suggesting that the rate of bilateral treatment is increasing. However, this analysis likely underestimates the proportion of patients with two eyes treated, as patients may have received bilateral treatment without being dispensed a quantity of two. For example, if 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, if they are supplied an injection of aflibercept and an injection of ranibizumab at the same time, or if their two eyes are treated on alternate weeks or months. As authority approval for initial treatment of each eye must be

⁵ <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2007-03/pbac-psd-ranibizumab-mar07>

⁶ Caroline C. W. Klaver, Jacqueline J. M. Assink, Redmer van Leeuwen, Roger C. W. Wolfs, Johannes R. Vingerling, Theo Stijnen, Albert Hofman, and Paulus T. V. M. de Jong, Incidence and Progression Rates of Age-Related Maculopathy: The Rotterdam Study, *Investigative Ophthalmology & Visual Science*, September 2001, Vol. 42, No. 10

⁷ Klein R, Klein BEK, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: The Beaver Dam Eye Study. *Ophthalmology*. 1997;104:7–21.

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.

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. For incident patients, the number of injections of ranibizumab or aflibercept per patient appears to be broadly similar. Patients initiating AMD treatment between 1 December 2012 and 30 November 2013 used an average of 9.30 injections of ranibizumab and 8.28 injections of aflibercept. For continuing patients, those who switched to aflibercept had a higher average number of injections in the next 12 months (8.71) than those who remained on ranibizumab (6.90). There may be differences between patients who switch and those who remain on the same agent that could influence the number of injections used. For example a switch may occur due to failure to respond to one agent. Market dynamics, physician and patient preference may also influence the results.

Many factors have been identified in this report that suggest utilisation of aflibercept and ranibizumab for wet AMD will continue to increase strongly into the future. These factors include the increased risk of development and progression of AMD in the context of an ageing population, high rates of continuation on treatment and a high number of injections per patient per year. The DUSC agreed that overall utilisation increases into the future are likely for these reasons. In addition, the 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.

DUSC consideration

The DUSC considered the comprehensive responses provided by sponsors, the Macular Disease (MD) Foundation of Australia, and the Royal Australian and New Zealand College of Ophthalmologists (RANZCO). Information and advice provided in these responses included:

- the importance of treating wet AMD for improving visual outcomes and quality of life;
- regimens used in clinical practice, including 'treat and extend' and prn regimens and how this may influence the number of injections;
- continuation rates and duration on treatment;
- rates of bilateral treatment;
- geographical variation in treatment rates and practice;
- extended clinical trials, cross over studies, and observational studies.
- education regarding safety, specifically the risk of stroke.

The DUSC noted that the average number of injections of aflibercept and ranibizumab in the first year of treatment for the group of patients initiating ranibizumab or aflibercept between December 2012 and November 2013 was considered 'similar' by the secretariat

report, and clinical and consumer groups, but the sponsor of aflibercept considered the difference of one injection to be clinically and financially significant.

The DUSC considered there has been insufficient time since aflibercept was listed to determine if the numerical difference of one injection between ranibizumab and aflibercept in the first year will continue in future cohorts of initiators in Australian clinical practice. The DUSC noted that utilisation patterns evolved over several years for ranibizumab with the average number of ranibizumab injections for initiating patients increasing from 5.7 for patients who initiated in 2007 to 8.3 for patients who initiated in 2011.

The DUSC also considered that there has been insufficient time since aflibercept was listed to determine whether the number of injections in the second and subsequent years of treatment will differ between the two drugs. The DUSC noted that for ranibizumab, the average number of injections has varied in each year of subsequent treatment for initiating groups of patients. Given the high rates of continuation and long duration on treatment the DUSC noted that use in second and subsequent years drives much of the utilisation and cost. The DUSC also noted that examining injection patterns in the second and subsequent years of prevalent treated patients who initiated on ranibizumab and then either remained on ranibizumab or switched to aflibercept is likely confounded. For example, patients who remain on the same treatment may be responding and stable whereas patients who switch may have inadequate response. The reasons for switching cannot be ascertained from PBS data. The DUSC considered that there are likely to be many other known and unknown confounders that make it difficult to attribute any differences in patterns of use to differences between the medicines themselves. For example, the DUSC considered that prescriber preference could be one further factor influencing patterns of use.

The DUSC noted that the sponsor of aflibercept provided results from a 10% PBS sample indicating that continuation rates are higher for aflibercept than ranibizumab. The DUSC considered that the high proportion of censoring due to the short follow-up time available emphasises limitations of such analyses.

The DUSC noted the various clinical trial extension studies, cross-over studies and observational studies, referenced in stakeholder responses. The DUSC considered that three observational studies undertaken with United States administrative data (Ferreira 2013⁸, Johnston 2013⁹, and Turpcu 2014¹⁰) show no significant differences in the number of aflibercept and ranibizumab injections used in practice.

Overall, the DUSC reiterated that additional observation time is required before it is possible to confidently assess, in Australian clinical practice, whether there is a difference in

⁸ Ferreira A, et al. Treatment Patterns of Ranibizumab and Aflibercept for the Management of Wet Age-Related Macular Degeneration in Routine Clinical Practice in the United States. *Value in Health*. 2013;16:A512.

⁹ Johnston SS, et al. Retrospective Analysis of First-Line Anti-Vascular Endothelial Growth Factor Treatment Patterns in Wet Age-Related Macular Degeneration. *Adv Ther*. 2013;30:1111-1127.

¹⁰ Turpcu A, et al. Patterns of Anti-VEGF Use in Neovascular Age-Related Macular Degeneration: A United States Administrative Claims Database Analysis. *Value in Health*. 2014;17:A285.

the number of injections of aflibercept and ranibizumab, the magnitude and direction of any such difference, and whether this translates to a difference in outcomes.

The DUSC considered that there have been higher continuation rates and longer durations on treatment than anticipated. The DUSC noted that there was limited information available at the time that the PBAC recommended the listing of ranibizumab. The recommendation was based on clinical trials of one or two year durations and a modelled economic evaluation with a time horizon of 5 years. Several factors were raised by stakeholders that may account for this including increasing awareness of the disease and earlier treatment, second eye progression, continued benefit from treatment, and that very few patients can stop treatment altogether. The DUSC considered that utilisation increases into the future are likely given the ageing population and current utilisation patterns.

The DUSC noted 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. The response from the RANZCO provided an assessment of the number of ophthalmologists per 100,000 by State showing a correlation with utilisation. Differences may also be due to variations in clinical practice and awareness of AMD. The Secretariat will provide a copy of the DUSC report and relevant stakeholder input to the Medicare Benefits Division and Health Workforce Division of the Department of Health.

Actions undertaken by the DUSC Secretariat

A copy of the report was provided to the Sponsors of aflibercept and ranibizumab, the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) and the Macular Disease Foundation Australia for comment prior to consideration by the DUSC.

DUSC actions

The DUSC requested that the report and advice be provided to the PBAC.

The DUSC may wish to review use of AMD medicines when a further 2 years of data are available for aflibercept. The DUSC commented that:

- a separate analysis of average aflibercept and ranibizumab injections/patient/year for different initiation years would be informative; and
- extraction of treated eye data would assist in interpretation of utilisation 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.

Sponsors' comments

- Bayer Australia Ltd
Bayer thanks the DUSC for the opportunity to respond to the analysis and for its consideration of our response.
- Novartis Pharmaceuticals Australia Pty Limited
No comment provided.

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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