



**Australian Government**

**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1310 – Optical coherence tomography to inform treatment with aflibercept***

**Sponsor/Applicant/s:**                    **Bayer Australia Pty Ltd**

**Date of MSAC consideration:**   **1 August 2013**

#### **1. Purpose of application**

In May 2012, the Department of Health and Ageing received an application from Bayer Australia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of optical coherence tomography (OCT) to measure central retinal thickness (CRT) to initiate and monitor PBS-subsidised use of aflibercept for the treatment of macular oedema following central retinal vein occlusion (CRVO).

Bayer also submitted a corresponding major submission to the July 2013 Pharmaceutical Benefits Advisory Committee (PBAC) meeting requesting to extend the current Authority required Pharmaceutical Benefits Schedule (PBS) listing for aflibercept to include sole subsidised treatment of patients with macular oedema caused by CRVO.

The co-dependent applications relate to OCT for the measurement of CRT, which informs a patient's eligibility for treatment with aflibercept and then response in terms of improved/maintained visual acuity (VA) and quality of life.

OCT is a non-contact, non-invasive high resolution imaging technique that provides cross-sectional tomographic images of the ocular microstructure through the thickness of the retina. OCT provides a quantitative anatomic representation of the axial fluid distribution within the layers of the retina, and hence a specific measurement of retinal thickness. It is analogous to ultrasound, measuring the back-reflection intensity of infrared light rather than sound.

There are two main types of OCT available, A-scans acquired in the time domain (TD) and the newer B-scans acquired in the spectral frequency domain (SD). OCT systems are stand-alone mobile equipment with no specific complementary services required.

As a result of providing detailed information on the architectural morphology of the retina on the level of individual retinal layers, OCT has been proposed to detect early pathological changes, even before clinical signs or visual symptoms occur. There is no reference standard

against which OCT can be measured. OCT has been proposed as a new ‘gold standard’ structural test for retinal abnormalities.

OCT is currently MBS funded for partial coherence interferometry for lens surgery – Item numbers 11240, 11241, 11242 and 11243.

OCT is widely used in Australia, to evaluate patients treated for macular oedema and CRVO. It is used as a baseline measurement against which to assess the severity and extent of oedema and in the context of assessing the impact of treatment changes in oedema

Retinal vein occlusion (RVO) is a common cause of visual loss, caused by an obstruction of the retinal venous system, most commonly involving occlusion of a branch retinal vein (BRVO) or the central retinal vein (CRVO) (Laouri et al 2011). Thrombus formation may be the primary cause of occlusion, however other possible causes include external compression or disease of the vein wall e.g. vasculitis (Laouri et al 2011). Secondary to vein obstruction, retinal ischemia occurs and signals the release of vascular endothelial growth factor (VEGF), which in turn destabilizes the endothelial tight junctions and promotes endothelial cell proliferation. CRVO is classically characterised by macular oedema, increased dilation and tortuosity of all retinal veins, retinal oedema cotton wool spots, areas of capillary non-perfusion, widespread deep and superficial haemorrhages (Coscas et al 2011).

## **2. Background**

A previous assessment of OCT for the diagnosis and monitoring of macular disease and glaucoma was considered by MSAC in November 2008 (application 1116). MSAC then advised not to publicly fund OCT with respect to these indications due to insufficient evidence to support the clinical claims.

The proposed indication for the current application is narrower than those considered in the previous MSAC assessment.

## **3. Prerequisites to implementation of any funding advice**

OCT devices for retinal and macular imaging are listed on the Australian Register of Therapeutic Goods (e.g. ARTG number 194817 and 197023), and classified Class IIa indicating a low level of risk.

Several prior tests are required before OCT is performed. A range of baseline ophthalmic assessments would be followed by fundus photography and/or fundus fluorescein angiography (FFA) in order to confirm a diagnosis of CRVO and the extent of damage to the macula/retina. Fundus photography permits the clinician to identify the area of retinal thickening and haemorrhage, whereas FFA identifies the presence and area of fluorescein leakage and capillary non-perfusion. These tests also determine the presence or absence of macular oedema. Finally, OCT then measures retinal thickness, providing a quantitative assessment of the severity of macular oedema.

#### 4. Proposal for public funding

##### Proposed MBS item descriptors for OCT for the measurement of CRVO for determining the eligibility of aflibercept and monitoring aflibercept

###### **Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS**

Xxxx

Optical coherence tomography for the assessment of central retinal thickness to determine the eligibility for PBS-subsidised aflibercept of a patient with macular oedema secondary to central retinal vein occlusion.

Fee: \$250.00 Benefit: 75% = \$187.50 85% = \$212.50

Xxxx

Optical coherence tomography for the assessment of central retinal thickness to determine whether to modify therapy with PBS-subsidised aflibercept in a patient with macular oedema secondary to central retinal vein occlusion.

Fee: \$250.00 Benefit: 75% = \$187.50 85% = \$212.50

###### Explanatory notes

Diagnosis of macular oedema secondary to central retinal vein occlusion by professional attendance of an ophthalmologist is required. It will involve the use of standard assessments, including but not limited to retinal photography with intravenous dye injection (items 11215 and 11218).

Determination of aflibercept eligibility requires both baseline and ongoing assessment using optical coherence tomography.

The joint ESCs had concerns that, despite the PICO and the applicant's submission frequently referring to a retinal thickness of  $\geq 250$   $\mu\text{m}$ , there is no mention of this in the proposed MBS item descriptors.

The joint ESCs also advised that, given that evidence showed that visual acuity was a more significant measurement of both need for treatment and evidence of treatment responsiveness than OCT, and if there were to be two MBS items, then the appropriate level of visual acuity would need to be incorporated into the initial and subsequent MBS item descriptors. The joint ESCs noted that the clinical algorithm provides for OCT being undertaken in patients with visual acuity  $< 20/40$ , but this has not been included in the MBS item descriptor.

##### Proposed PBS restriction to extend the listing of aflibercept

###### **Authority required**

Initial treatment by an ophthalmologist, as the sole subsidised therapy, for a patient newly diagnosed with macular oedema caused by central retinal vein occlusion (CRVO) who:

- a) has confirmed presence of central retinal thickening on OCT
- b) presence of documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (EDTRS) chart.

Initial treatment with monthly injections for up to 6 months followed by OCT guided treatment.

###### **Authority required**

Continuing treatment by an ophthalmologist, as the sole subsidised therapy, for macular oedema following CRVO where the patient has previously been granted an authority prescription for the same eye.

The proposed MBS listing seeks to restrict the service to ophthalmologists as the subsequent medical management in the context of treating CRVO would require the clinical expertise of an ophthalmologist.

## **5. Consumer Impact Statement**

Given the proposal to restrict the service to ophthalmologists, and that most of these specialists work in urban areas, there is likely to be limited access to specialist care of CRVO (OCT monitoring and any intravitreal treatment) in outer regional, remote and very remote areas (AIHW 2009).

## **6. Proposed intervention's place in clinical management**

The claimed utility of OCT is for assessing macular oedema secondary to CRVO in order to identify patients who would benefit most from initial and ongoing treatment with aflibercept. In this capacity, it is not intended as a technology that can replace the ophthalmological testing which enables diagnosis of CRVO.

The clinical algorithm indicated that all patients with a diagnosis of macular oedema secondary to CRVO and visual acuity <20/40 will receive OCT testing. This did not concur with the proposed MBS item descriptor nor the proposed PBS restriction, which do not specify a specific level of visual acuity.

The MBS item descriptor did not mention visual acuity and the requested PBS restriction specified that patients have documented impairment of best corrected visual acuity (BCVA) on the ETDRS. Following initial treatment of monthly aflibercept injections for 6 months patients, will then receive OCT to determine the need for and timing of re-injection of aflibercept. Neither the proposed MBS listing nor PBS restriction specified criteria for continuation of therapy.

## **7. Other options for MSAC consideration**

Nil.

## **8. Comparator to the proposed intervention**

The submission nominated OCT with best supportive care as the main comparator to OCT with aflibercept.

The comparators defined in the DAP were not used by the submission:

- ranibizumab as part of standard medical management which involves prior diagnostic tests, but not OCT. The submission did not use this comparator because all clinical trials presented in the submission included OCT.
- aflibercept informed only by currently funded diagnostic tests, i.e., without the use of OCT (requested by PASC). The submission did not use this comparator because all clinical trials included OCT.

The submission argued that no comparisons can be made to treatment without use of OCT given the lack of trial evidence. The submission indicated that while the available evidence (all trials using OCT) does not specifically address the requested comparison, a linked evidence approach was presented.

MSAC assessed the provided evidence with the objective of deciding whether funding OCT for the requested purposes was justified compared to not funding or using OCT.

## 9. Comparative safety

The submission did not provide an assessment of the comparative safety of OCT. The submission stated that OCT is considered a non-invasive ophthalmic test and is considered a safe procedure. The submission did not quantify the claim of comparative safety.

## 10. Comparative effectiveness

Three of the nine test/re-test studies provided results for the coefficient of repeatability. The remaining six studies provided results relevant to intra-class repeatability.

The submission drew the following conclusions on the basis of the test/re-test results.

- There is high intra-class repeatability within the TD and SD OCT systems. Therefore, within the same class of machine, OCT is an objective and reliable tool to measure OCT and quantitate treatment-related differences. The intra-class repeatability observed in the included studies was based on patient populations that are not applicable to the proposed MBS and PBS populations – only 4 of the 9 studies included patients with CRVO and the proportion of CRVO patients was generally small, i.e. <10%. The studies also had small numbers, limiting the power of the study and strength of the conclusions drawn.
- Four studies found low agreement between macular thickness measurements of different OCT systems. The submission stated that any potential differences across OCT systems are unlikely to impact on individual patient treatment and outcomes. The submission made this claim on the basis that practices are unlikely to switch OCT systems and therefore all of a patient's CRT measurements would be done using the same OCT system. That is likely if a patient remains at the same practice, but it is also likely that patients may relocate and potentially be assessed using a different OCT system.

Based on the 14 studies assessing the correlation between CRT and visual acuity, the submission drew the following conclusions.

- Ten of the 14 studies reported a significant inverse relationship with either baseline CRT or final visual acuity; changes in CRT and final visual acuity; and retinal changes visible on OCT and visual acuity outcomes.
- Overall, there is a modest but significant relationship between retinal thickness changes and visual acuity outcomes.

The study results did not strongly support this claim, for the following reasons.

- While there was a statistically significant inverse relationship between baseline CRT and final visual acuity in Hoeh et al (2010), the authors of the paper indicate that some patients recovered good visual acuity, others suffered regular recurrences of macular oedema or failed to show visual improvement despite resolution of macular oedema. The authors conclude that the association of CRT with visual acuity seems to be modest, suggesting that other factors have a stronger impact on visual acuity than CRT.
- Lima et al (2010) suggest that CRT alone should not be used as the only predictor of visual outcome in patients with CRVO, and that OCT and fluorescein angiography together provide a more complete assessment of patients with CRVO.
- All studies, with the exception of Scott et al (2011), have small sample sizes. Scott et al (2011) concluded that the correlation coefficient for association between baseline OCT-measured centre point thickness and BCVA is modest (-0.27; 95% CI: -0.38, -0.16).

Overall, the results provide weak support for a significant correlation between change in CRT and change in visual acuity.

The submission also provided a qualitative assessment of the use of OCT as a monitoring test. This assessment was based on the opinion of one ophthalmologist. The submission

concluded that OCT is valuable as a monitoring test for treatment with aflibercept. The submission did not have an evidentiary base for this claim. No evidence was presented in the trial reports or additional studies included in the MSAC part of the co-dependent submission which support the use of OCT as a monitoring test for treatment with aflibercept.

## 11. Economic evaluation

A modelled economic evaluation (cost-utility analysis) based on superiority claim for comparative benefit of OCT with aflibercept was presented.

The submission's model assumed that consultations and OCT occur in a 1:1 ratio to injections, which makes no allowance for monitoring services that do not result in re-injection but where a decision is made to review for further injection at a subsequent appointment. Therefore, the model understated the cost of monitoring.

MBS listing of OCT represents a 'pre-requisite' for the proposed PBS listing of aflibercept due to the co-dependency relationship with aflibercept. OCT does not directly generate health outcomes; rather, its MBS listing would allow aflibercept to be accessible and the effectiveness of aflibercept would give additional health outcomes in terms of visual acuity and quality-adjusted life-years (QALYs).

The MBS item relevant to the administration of aflibercept under the proposed indication is presented below.

### MBS item associated with administration of aflibercept

MBS code	Description and benefit
42740	INTRAVITREAL INJECTION OF THERAPEUTIC SUBSTANCES, or the removal of vitreous humour for diagnostic purposes, 1 or more of, as a procedure associated with other intraocular surgery. Fee: \$300.75 Benefit: 75% = \$225.60 85% = \$255.65

A summary of unit costs in the economic evaluation is presented below.

### Summary of unit costs in the economic evaluation

Resource item	Base case	Source
Acquisition of aflibercept per injection	\$1,150.00	Proposed PBS price
Administration of aflibercept injection	\$300.75	MBS fee for intravitreal injection
OCT measurement of retinal thickness per test	\$250.00	Proposed MBS fee

OCT is currently funded on the MBS for another indication (i.e., services related to lens surgery under items 11240 and others) at \$81.45 per test.

## 12. Financial/budgetary impacts

### Likely number of eyes tested and treated

The estimated number of patients (eyes) treated as well as estimated number of OCT tests was provided.

The number of OCT tests is likely underestimated given it is based on the number of injections observed in the trials and does not account for the fact that patients will have more OCT tests than injections.

The table below shows the estimated number and cost to the MBS of injections and OCT tests. These are likely to be underestimates given the assumptions used to estimate uptake, injection frequency and use of OCT.

Total aflibercept administration costs and OCT test costs to the MBS were estimated to be \$1.6 million in Year 1, increasing to \$4.8 million by Year 5. Sensitivity analyses conducted during the evaluation demonstrated that increasing the frequency of OCT to monthly following the first 6 months of aflibercept treatment would increase these MBS costs to \$2.4 million in Year 1 up to \$11.5 million in Year 5.

### **13. Key issues for MSAC from ESC**

#### Main issues around the evidence and conclusions for safety

The ESCs did not disagree with the safety of the OCT procedure, but noted that no evidence had been provided to support this claim.

#### Main issues around the evidence and conclusions for clinical effectiveness

The association between OCT, as a surrogate process measure to assist with treatment management, and the clinical outcome of visual acuity remains unclear. This makes it difficult to assess whether the use of OCT improves the management of aflibercept and thus contributes to improving health outcomes for patients.

Whether the evidence presented by the submission regarding the use of OCT for monitoring, based on the opinion of one ophthalmologist, supports the submission's assertion of the value of OCT for improving treatment.

#### Other important clinical issues and areas of clinical uncertainty

The joint ESCs noted that the diagnosis of macular oedema secondary to central retinal vein occlusion does not depend on OCT; however OCT assists clinicians to determine the treatment. The extent of co-dependence of aflibercept and OCT needs further assessment to determine what contribution OCT makes to treatment and management of CRVO.

#### Main economic issues and areas of uncertainty

There is no provision in the economic model to consider the implications of the accuracy of OCT for aflibercept. The Joint ESCs were concerned that the accuracy of OCT was not based on the most current technological version of OCT and the difference between 2D and 3D OCT could have a significant impact on the validity of treatment response measurements between specialists. Given the proposal to use OCT as an ongoing monitoring tool, the ESCs advised that the sensitivity and specificity of OCT in the monitoring of response to VEGF inhibitor therapy should have been presented. This was further exacerbated by the evidence presented for repeatability, which was not in patients with CRVO.

The ESCs were also concerned that the submission has not presented evidence to support the claim that OCT is considered to be "gold standard" for monitoring of macular oedema secondary to CRVO. The ESCs concluded that, based on the evidence presented in the submission, visual acuity was of more significance as a measurement of treatment response than change in the retinal thickness as measured by OCT. This mirrors the place of OCT in the clinical management algorithm.

#### Main financial issues and areas of uncertainty

The submission did not provide any sensitivity analyses of the estimated use and financial implications of the listing of aflibercept and OCT.

However, there are a number of issues in the financial analysis that suggest the results significantly underestimate the costs to the PBS/RPBS and MBS. In particular:

- the assumption of (**redacted information**)% uptake in Year 1 may not represent 'high uptake', particularly given that there is currently no other PBS-listed treated for macular oedema secondary to CRVO
- OCT costs are likely to be underestimated due to the inappropriate assumption of a 1:1 ratio of injection for incidence of these costs
- the estimated number of OCT tests may not be accurate given it is based directly on the number of injections given, whereas, following the first year of treatment, OCT will not always identify a need for a re-injection
- the failure to include baseline eligibility criteria for CRT may not be reasonable, given that such an omission would open up treatment to patients for whom there is no clinical evidence and likely result in much greater uptake than estimated
- the failure to include re-injection criteria may not be reasonable given that, without such criteria, the value of OCT monitoring is limited or has no direct link to aflibercept treatment.

#### **14. Other significant factors**

MBS items 42738, 42739, 42740 are used by ophthalmologists for the injection of therapeutic substances into the eye. The PBS listing of ranibizumab for the treatment of age-related macular degeneration in 2007 (and more recently aflibercept) accounts for almost all of the current utilisation of these items.

#### **15. Summary of consideration and rationale for MSAC's advice**

MSAC noted that the July 2013 PBAC meeting did not recommend that aflibercept, the co-dependent technology in this submission-based assessment for OCT, be listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of central vein retinal occlusion (CRVO).

MSAC recalled that, at its April 2013 meeting, it had considered a referral from PBAC for advice in relation to OCT in CRVO and branch vein retinal occlusion (BRVO) for access to ranibizumab (Application 1350), a competing anti-VEGF medicine. MSAC had advised then that it intended to consider OCT in RVO in the context of both aflibercept and ranibizumab, and to consider both identified purposes of OCT (determining eligibility for anti-VEGF treatment and subsequent monitoring).

MSAC also recalled that, at its November 2008 meeting, it had not supported public funding of OCT for the diagnosis and monitoring of macular disease and glaucoma (Application 1116), but acknowledged that OCT is already widely used in the management of macular disease. This widespread use of OCT without MBS funding is the source of complaints about out-of-pocket costs from patients, who are mostly elderly. MSAC also noted that whilst the ophthalmologists have provided strong expert opinion in support of MBS listing, the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) does not have any immediate plans to re-submit an application for MSAC assessment of OCT.

MSAC agreed with its Protocol Advisory Sub-Committee (PASC) and its Evaluation Sub-Committee that OCT is not essential to the diagnosis of RVO, but that the basis of the identified codependency with anti-VEGF medicines were its roles both in assessing oedema before using treatment and also in monitoring treatment. MSAC agreed with the advice of PASC on pages 21 and 22 of the DAP that different types of evidence addressing four main questions would be needed to consider these two roles. MSAC also agreed with the advice of PASC with reference to Bell et al 2009, 2010 that the monitoring role needs more evidence. This is reasonable because this role would generate more costs given the repeated use of OCT, and would potentially generate more efficient use of anti-VEGF treatment.



In relation to the role of OCT in assessing oedema before using treatment, MSAC noted that an OCT-determined threshold for central retinal thickness (CRT) of  $\geq 250\mu\text{m}$  was included in the participant eligibility criteria of both the two key randomised trials of aflibercept (COPERNICUS and GALILEO). The results from these trials provide the evidence base that aflibercept is effective in patients above this threshold. However, as noted by the submission, this also means that there is no evidence base examining whether aflibercept is effective in patients below this threshold. Taken together, these trials do not provide evidence to address the first question listed in the DAP in relation to the performance of OCT at baseline in predicting any variation in the magnitude of effectiveness of aflibercept above and below this eligibility threshold. This absence of evidence is not unique in clinical practice; MSAC noted that trials of medicines in heart failure using echocardiogram-based thresholds were similarly unable to provide evidence of the performance of echocardiograms in predicting any variation in treatment effect above and below the trial eligibility thresholds. MSAC further noted that this same issue also applies to the eligibility criteria related to baseline visual acuity in the treated eye or time between diagnosis and study initiation. However an application for MBS funding is not needed to support the implementation of these other eligibility criteria in clinical practice.

MSAC also reviewed the 14 provided studies which examined associations between baseline CRT and final visual acuity, between change in CRT and final visual acuity, or between retinal changes visible on OCT and visual acuity outcomes. MSAC noted that all studies were small (sample sizes ranging from 10 to 61) with one exception (Scott et al (2011), with a sample size of 271). The correlation coefficient reported for this study for the association between baseline OCT measured centre point thickness and best-corrected visual acuity (BCVA) of -0.27; 95% CI: -0.38, -0.16 is broadly consistent with the results of the other studies: the association is modest with a small negative coefficient, but statistically significant.

MSAC agreed with the applicant that an OCT assessment at baseline before treatment would also be a necessary pre-requisite should OCT prove to have a subsequent monitoring role to guide the need for and timing of subsequent aflibercept re-injections.

In relation to the role of OCT in monitoring, MSAC addressed the three remaining questions listed in the DAP. The second question addresses whether there is an association between change in central retinal thickness and change in visual acuity. MSAC considered that the data collection in the two key randomised trials of aflibercept would provide more compelling evidence to address this question than the 14 studies provided. For example, referring to the Brown et al 2013<sup>1</sup> publication of the 1-year results from COPERNICUS, MSAC compared the two outcomes and concluded that the onset of effect of aflibercept on CRT followed a similar time course to the onset of its effect on BCVA. This was particularly evident after randomisation in the aflibercept arm. The smaller effect after cross-over at 24 weeks in the sham arm was consistent, but less marked.

The third question addresses whether OCT measurement of CRT is reliable. MSAC noted that a number of studies with small sample sizes were provided assessing both within instrument (intra test/re-test) reliability and between instrument (inter test/re-test) reliability across a number of ocular conditions to support the applicant's conclusions of high within instrument reliability and low between instrument reliability in CRVO. Although consistent

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<sup>1</sup> Brown D.M., Heier J.S., et al. Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study. American Journal of Ophthalmology, 2013 Article in Press.

with the claims, MSAC considered that this evidence base was sparse for CRVO. Given the conclusion of low between instrument reliability, MSAC also noted that the Stratus Time Domain OCT instrument was used in both trials of aflibercept (to form the 'evidentiary standard'), and that the applicant had advised that this instrument is currently used in Australia.

The fourth question addresses whether the proposed response criteria can detect true between individual variation in treatment effects. MSAC noted that the applicant chose not to nominate any threshold eligibility or response criteria because of the conclusion of low between instrument reliability.

MSAC agreed that OCT is a non-invasive ophthalmic test and can be considered a safe procedure.

MSAC considered that OCT costs much less per patient than aflibercept or its injection if used only once per patient. Repeated use for monitoring purposes would increase its costs but not exceed the costs of the medicine. However, MSAC also noted that the modelled economic evaluation did consider the implications for aflibercept of the accuracy of OCT.

Using the applicant's proposed OCT fee, the estimated net costs to the MBS (\$1.6 million in year 1, increasing to \$4.8 million in year 5) and the PBS (**redacted information**) reflect the relative costs of OCT, aflibercept and injections. The estimates of OCT costs to the MBS include both its initial assessment and monitoring roles.

In summary, MSAC concluded that, in CRVO, the initial assessment role of OCT was possibly justifiable by the entry criteria and the aflibercept response shown in the randomised trials of aflibercept, but the monitoring role of OCT was unsubstantiated.

MSAC anticipated that the corresponding PBAC decision not to recommend aflibercept would likely result in a resubmission, and so considered what additional analyses of existing data might be presented in a resubmission to provide a more substantive evidence base for these roles.

In relation to an initial assessment role for OCT:

- any evidence of either (i) a good prognosis or (ii) a poor prognosis that is impacted by the effectiveness of aflibercept in CRVO patients with a CRT below the threshold of 250µm using the Stratus Time Domain OCT instrument (or confirmation that there is no such evidence, for example, that none of the Phase I or II trials of aflibercept in CRVO included such patients)
- evidence to assess whether varying baseline CRT varies the prognosis of BCVA, using individual patient data from the sham arms of COPERNICUS and GALILEO
- evidence to assess whether varying baseline CRT varies the prognosis of aflibercept-treated BCVA, using individual patient data from the aflibercept arms of COPERNICUS and GALILEO.

In relation to a monitoring role for OCT:

- evidence to assess whether a change in individual CRT is associated with a change in individual BCVA, both contemporaneously (ie comparing changes at the same time points) and predictively (ie comparing an early change in CRT with final change in BCVA), using individual patient data from the aflibercept arms (and potentially also from the sham arms following cross-over to aflibercept) of COPERNICUS and/or GALILEO,

presented as a plot of change in CRT in the x-axis against change in BCVA in the y-axis and corresponding statistical analysis of correlation

- evidence to assess the co-efficient of variation of CRT results within untreated patients, e.g., using individual patient data from the sham arms of COPERNICUS and/or GALILEO
- evidence to assess the change in CRT (both short- and long-term) with aflibercept and its variance, e.g., using individual patient data from the aflibercept arms of COPERNICUS and/or GALILEO.

MSAC referred to the two articles by Bell et al<sup>2</sup> cited in the DAP for further guidance on appropriate methods of these analyses.

In keeping with its April 2013 advice, MSAC considered that assessment of both these roles of OCT should be enhanced by having each analysis replicated for ranibizumab in CRVO (with reference to the CRUISE randomised trial of ranibizumab) and for ranibizumab in branch retinal vein occlusion (with reference to the BRAVO randomised trial of ranibizumab).

## **16. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of optical coherence tomography (OCT) for assessment of central retinal thickness in the presence of macular oedema secondary to central retinal vein occlusion for access to aflibercept, MSAC advises that it does not currently support public funding because of insufficiently presented evidence in relation to its roles in assessing oedema before using treatment and also in monitoring treatment and thus in relation to its cost-effectiveness.

MSAC advised that existing data, appropriately analysed, would usefully inform a re-consideration.

MSAC proposed that it would convene a stakeholder meeting in conjunction with PBAC to progress OCT-related applications, including by determining what data would help inform MSAC and PBAC. The stakeholder meeting should include ophthalmologists, consumers, OCT providers and the pharmaceutical companies who are lodging and planning applications for medicines to treat ocular diseases and which involve the use of OCT.

## **17. Applicant's comments on MSAC's Public Summary Document**

No comment.

## **18. Context for decision**

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

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<sup>2</sup> Bell, K. J., Hayen, A. et al (2009). 'Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data', *BMJ*, 338, b2266.

Bell, K. J., Irwig, L. et al (2010). 'Should response rules be used to decide continued subsidy of very expensive drugs? A checklist for decision makers', *Pharmacoepidemiol Drug Saf*, 19 (1), 99-105.

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

## **19. Linkages to other documents**

MSAC's processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).