Australian Government

Medical Services Advisory Committee

Public Summary Document

Optical Coherence Tomography (OCT) – Assessment of investigative medical services for monitoring

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose

To review the draft paper for publication *value of OCT for monitoring central retinal vein occlusion (CRVO) treated with ranibizumab* and the accompanying document entitled *using 'best test' criteria to decide on subsidy of monitoring tests*.

2. MSAC's advice to the Minister

After considering the strength of the draft paper analysing clinical validity and detectability of response when using OCT to monitor CRVO, MSAC supported public funding for a new MBS item for OCT, in conjunction with other diagnostic services, to help determine the presence of macular oedema and thus eligibility for PBS-subsidised medicines for PBS-eligible macular conditions.

MSAC advised that this support was conditional on the estimated total financial cost being provided to the next MSAC Executive meeting. MSAC also advised that there should be a limit of no more than one OCT service per patient per year to help make the diagnosis of macular oedema in a macular condition.

MSAC upheld its previous advice that the MBS item descriptor should not allow for monitoring with OCT to assess post-treatment response, noting that this is better determined by a visual acuity test using a Snellen or early treatment diabetic retinopathy study (ETDRS) chart.

3. Summary of consideration and rationale for MSAC's advice

MSAC reviewed the results for clinical validity and detectability of response when using OCT to monitor CRVO from a paper submitted for publication by a team led by the Screening and Test Evaluation Program (STEP) group, and subsequently published as Bell et al (2017) *Retina* 37:509-514 (https://journals.lww.com/retinajournal/fulltext/2017/03000/EARLY_CRT_MONITORING_USING_TIME_DOMAIN_OPTICAL.13.aspx). These results were generated from individual patient data extracted from the main randomised controlled trial of intra-vitreal ranibizumab in CRVO (the CRUISE study). MSAC noted that, for central retinal thickness (CRT) to be

useful to monitor the effect of ranibizumab, it would need to have incremental value beyond just monitoring best corrected visual acuity (BCVA). MSAC noted that the results indicated that BCVA outperformed CRT (assessed using time-domain OCT) in terms of the more important clinical validity criterion, and that adding CRT information to BCVA did not improve clinical validity. Although the detectability of response criterion tended to be better for CRT than BCVA at 1 week and 1 month, these were equivalent for CRT and BCVA at 6 months, and, in the context of the clinical validity results, these responses do not have major clinical relevance. MSAC considered that these results were likely to apply to CRT assessed using spectral-domain OCT. Consistent with its conclusions in April 2015 in the context of diabetic macular oedema and dexamethasone implant, MSAC concluded that these results did not support a monitoring role for OCT in CRVO.

However, MSAC noted that CRT did have incremental value and clinical validity in the sham treated group, providing some support to using OCT to diagnose the presence of macular oedema in macular conditions, particularly given the more invasive nature of fluorescein angiogram which, although more expensive, is currently stipulated to diagnose these macular conditions in the relevant PBS restrictions. However, MSAC was concerned about the repeated use of OCT for a patient over time to re-confirm the continuing presence of macular oedema across those macular conditions where treatments are available, and thus uncertainty about the number of OCT services that might be rendered each year to a patient. Such repeated use might be difficult to distinguish from monitoring. Thus MSAC was uncertain about the financial cost of supporting OCT for diagnosis and whether this cost could be incorporated within some other MBS item(s) involving a medical service rendered by an ophthalmologist. MSAC therefore also requested that the Department advise the MSAC Executive of any unexpected implementation issues.

In relation to the general use of this approach to assessing investigational medical services intended for monitoring, MSAC agreed that it should be considered as an option when there is no direct evidence of effect on health outcomes. MSAC supported the preference for analyses to be based on individual patient data from relevant randomised trials. MSAC considered that more experience across a wider range of monitoring technologies would be valuable, especially given that an unusual feature in this instance was that one of the tests (BCVA) was also the patient-relevant endpoint, which meant that the results of the analyses were not surprising, and might have been different if a different endpoint were used. MSAC noted that this amount of evidence for a monitoring test is still unusual, and would be difficult to obtain for many current monitoring tests.

MSAC noted that the research it had reviewed on monitoring CRT in CRVO using OCT had been submitted for publication, and emphasised the importance of having a clear link between this PSD of its considerations and the evidence supporting these considerations, such as a link to a website summary of the research (see link above).

4. Background

In August 2013, MSAC decided not to support application 1310 for OCT to monitor CRT in the context of treating CRVO with aflibercept (Eylea® from Bayer Australia Ltd). It linked this application to similar issues arising for the use of OCT to monitor CRT in the context of treating RVO and diabetic macular oedema (DMO) with ranibizumab (Lucentis® from Novartis Pharmaceuticals Australia Pty Limited). It proposed to convene a stakeholder meeting in conjunction with the Pharmaceutical Benefits Advisory Committee (PBAC) to progress OCT-related applications.

The stakeholder meeting was held on 10 September 2013. At the meeting, some of the manufacturers of the relevant ocular medicines expressed a willingness to investigate whether it would be feasible to access the relevant trial data and perform MSAC's requested re-analyses.

Following the stakeholder meeting, and on behalf of MSAC, the Department coordinated a project involving researchers from the Screening and Test Evaluation Program (STEP) group based at the University of Sydney, Novartis Pharmaceuticals Australia Pty Limited, and Numerus (the contract research organisation engaged by Novartis which performed the individual patient data analyses). The preliminary results of this project were provided in draft form while it was still under internal review before being submitted for peer-review publication in a leading ophthalmology journal. A shorter paper provided reflections from the STEP group about the potential for this approach to be used in future assessments of monitoring technologies. This acknowledged that, in addition to addressing the specific issues of using OCT to monitor CRT in the context of treating CRVO with ranibizumab, this project was a pilot assessing the broader usefulness of the approach for other monitoring contexts.

In April 2015, MSAC deferred the application 1377 for OCT to determine eligibility for a dexamethasone implant in adults with macular oedema associated with diabetic retinopathy and pseudophakia (an artificial intraocular lens), until PBAC makes a positive recommendation regarding the corresponding PBS listing for dexamethasone.

In the April 2015 meeting, MSAC expressed concerns about the:

- lack of evidence to support a CRT threshold and therefore using OCT to assess for the presence of oedema would be subjective
- reproducibility of OCT measurements between instruments
- appropriateness of OCT for monitoring, as the application did not address what value adding OCT to monitoring would have over visual acuity alone.

MSAC foreshadowed that, should PBAC recommend PBS listing for dexamethasone, it intended that the MBS item descriptor should allow for the use of OCT before the initial implant of dexamethasone and before each subsequent implant, in each case to confirm the presence of oedema and thus the suitability of proceeding to inject the implant. MSAC stated that the MBS item descriptor not allow for the use of OCT to assess the post-treatment response as this can best be determined by a visual acuity test using a Snellen chart. MSAC also foreshadowed that the MBS fee should be approximately $50 as suggested by the Evaluation Sub-Committee (ESC).

5. Key issues from ESC for MSAC

ESC noted the four STEP assessment elements as involving three technical factors:

- clinical validity
- detectability of response to treatment
- detectability of long-term change relative to background within-patient variability

and a non-technical factor:

- practicality.

Of these, ESC agreed that clinical validity was the most important factor: how well different results of the investigative technology predict different patient-centred outcomes.

Specific comments regarding OCT assessing CRT for ranibizumab in CRVO

ESC noted that the Minister had announced the listing of ranibizumab for RVO (and DMO) in the Pharmaceutical Benefits Schedule (PBS) following a positive recommendation by PBAC in 2014. ESC understood that, in relation to the use of OCT in determining eligibility for initial or continuing treatment, the restrictions for ranibizumab would be similar to the current restrictions for age-related macular degeneration (ARMD). For initial treatment, the main investigative test is a fluorescein angiogram to diagnose the condition, with OCT reserved alongside red free photography to make a diagnosis where a fluorescein angiogram is contraindicated. No further investigation is specified for continuing treatment.

ESC noted that the draft paper assessed the value of time-domain OCT for monitoring patients with CRVO treated with intra-vitreal ranibizumab in terms of:

- the clinical validity of CRT at 1 week and 1 month after starting ranibizumab therapy
- whether CRT has incremental value over best-corrected visual acuity (BCVA) in predicting short-term and long-term (at 6 months) response.

ESC further noted the reliance on individual patient data (IPD) involving 325 of the 392 participants randomised into the CRUISE trial (a Phase III trial of ranibizumab in CRVO) to assess the strength of association between CRT measurements using OCT and baseline-adjusted 6-month BCVA.

ESC summarised the main findings of the draft paper as follows:

- CRT appears to have some clinical validity in terms of predicting changes in visual acuity
- CRT has little incremental value over BCVA
- BCVA monitoring of treated CRVO patients thus appears more informative than OCT monitoring.

ESC noted that the draft paper concluded that "[t]here is no evidence to support monitoring with time-domain OCT after starting ranibizumab to treat CRVO, at least in addition to the information obtained from BCVA." ESC understood that time-domain OCT instruments had largely been superseded in Australia by spectral-domain OCT instruments, and that whilst these had similar within-instrument variability, there are systematic differences in CRT results across these two types of OCT instrument.

ESC noted that the assessment groups raised two issues specific to OCT assessing CRT for ranibizumab in CRVO:

- One group questioned the apparent reliance on absolute CRT without adjusting for baseline variation in CRT (despite adjusting for baseline variation in BCVA): STEP responded that CRT was fitted on the natural scale for simplicity after assessing assumptions for linear regression of normality, homogeneity of variances and linearity using graphical techniques and finding that these held for all covariates without the need for transformation.
- One group questioned the usefulness of CRT or BCVA as a basis for any PBS continuation restriction, given that both measures had a low signal to noise ratio at 6 months: STEP agreed that the detectability of response was equivalent by 6 months and the ratio for both was ≤1. ESC considered that this was relevant from a cost-

effectiveness perspective if achievement of an acceptable ICER relies on estimating a proportion of initiated patients discontinuing due to monitoring.

Comments regarding OCT for the purpose of monitoring in ocular conditions

ESC noted MSAC's supportive deferral of application 1377 – OCT in the context of initial and subsequent injections of dexamethasone implant for DMO – until such time as PBAC recommends the PBS listing of dexamethasone implant. ESC highlighted two aspects as relevant to the MSAC consideration of OCT for monitoring CRVO treated with ranibizumab:

- OCT should be used to confirm the presence of oedema in DMO (and thus the suitability of proceeding to inject the implant), and not to monitor the post-treatment response which is best determined by a visual acuity test
- any MBS fee for OCT should be approximately $50.

ESC considered that, in addition to considering the conclusions of the STEP draft paper, issues for MSAC consideration would include what conclusions could also apply to:

- other macular conditions involving oedema, including branch vein retinal oedema (BRVO), DMO and ARMD
- other VEGF inhibitors, including aflibercept
- other OCT instruments, including spectral-domain OCT.

Comments on the wider use of the STEP approach to assessing health technologies used for the purpose of monitoring

ESC noted that the assessment groups raised three issues on the wider use of the STEP approach:

- two groups raised the importance and practicality of relying primarily on IPD from randomised trials involving both a monitoring technology and a therapeutic intervention: STEP responded by agreeing that the detectability of treatment response and long-term change can only be done using IPD, and that the assessment involved collaboration and close working relationships across both participants' skill sets (statisticians, epidemiologists and clinicians) and participants' functions (the custodians of the data and the team doing the analysis)
- two groups raised concerns about the statistical resourcing required to conduct the analyses: STEP responded by agreeing that careful planning and sufficient time are needed to conduct the analyses and noting that, in most instances, more examples of working through the technical factors is needed to amass more experience
- one group asked how addressing the technical factors could be extended to estimating the extent of improvement in health outcomes attributable to the use of monitoring (eg by a "linked evidence" approach): STEP responded that the factors represented a first step to judging whether the test may be useful, and that direct evidence would be more persuasive than indirect or "linked" evidence. STEP also suggested that interim MBS finding could be linked with the generation of further evidence on improving health outcomes. ESC observed that STEP did not suggest how this evidence generation might best be designed.

ESC also noted the response from Novartis, which:

- agreed that the quality and quantity of evidence required would not usually be available to inform contracted assessments for MSAC

- raised the need to consider how better to engage both the provider of the monitoring technology and the provider of the co-dependent therapy in order to facilitate the assessment overall.

Overall, ESC advised that the STEP approach is important and is heading in the right direction. ESC agreed with the impression across STEP and most commentators that more experience is needed to consolidate the developments across a wider range of monitoring scenarios. In addition, ESC considered that further work would be needed to connect this approach to an ability to estimate the extent of improvement in health outcomes attributable to monitoring and thus an ability to estimate incremental cost-effectiveness. This further work should anticipate that the co-dependent therapy may not necessarily involve a medicine being considered for PBS listing.

6. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website