Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1370 – Assessment of the detection of vitreomacular traction (VMT) with or without macular hole (MH) by optical coherence tomography (OCT) to inform treatment with ocriplasmin

Applicant: **Alcon Laboratories (Australia) Pty Ltd**

Date of MSAC consideration: **MSAC 62nd Meeting, 26-28 November 2014**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

The co-dependent application requested:

- Medicare Benefits Schedule (MBS) listing of optical coherence tomography (OCT) for the determination of patient eligibility and for efficacy assessment of a single treatment with ocriplasmin; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of ocriplasmin for the treatment of vitreomacular traction (VMT) including those with full-thickness macular hole (FTMH).

2. MSAC's advice to the Minister

After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness of OCT for use in confirming the diagnosis of VMT prior to treatment with ocriplasmin, MSAC deferred the application for the requested MBS item until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) makes a positive recommendation regarding the corresponding PBS listing of ocriplasmin. MSAC advised that, if PBAC subsequently decides to recommend to the Minister that ocriplasmin be listed on the PBS for the treatment of VMT, then MSAC would support an expedited process of reconsideration. This process would be undertaken to ensure MSAC support for public funding of OCT is aligned with the circumstances recommended by PBAC.

MSAC foreshadowed that the explanatory notes to the MBS item descriptor should include a baseline assessment and an assessment of response to ocriplasmin treatment at 30 days. MSAC also foreshadowed that the MBS fee should be $54.55 as suggested by ESC.

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

VMT is uncommon, symptomatic and progressive predominantly affecting the elderly where the current treatment is vitrectomy. MSAC noted that the application to list OCT in the MBS was part of an integrated co-dependent submission, which also requested that PBAC consider listing ocriplasmin in the PBS to treat VMT. In this context, three purposes were identified for OCT:

- confirm the diagnosis of VMT before treatment
- ensure that any macular hole (MH) is less than or equal to 400 μm in diameter before treatment
- assess response to treatment.

MSAC agreed that the appropriate comparator for OCT in this context is not using OCT. Although OCT is already widely disseminated in Australia, an assessment of its clinical and economic performance was considered necessary to advise whether it should be funded via the MBS.

OCT was considered to be a non-invasive, non-contact ophthalmic test and was therefore considered to be a safe procedure.

Overall, the data available suggested that OCT detects more cases and provides additional information with respect to diagnosing and staging VMT, macular hole (MH) or epiretinal membrane (ERM) compared with biomicroscopy, with or without other clinical investigations:

- VMT was identified in 6% of eyes assessed by retinal photograph and 21% of eyes by OCT, with 14% more patients recommended for vitrectomy following OCT (Do, 2007; N=84)
- VMT was identified in 8% of eyes assessed by retinal photograph and 30% of eyes by OCT (Gallemore, 2000; N=132)
- MH was graded more severely with OCT than with retinal photographs (Ullrich, 2002; N=94).

However, MSAC noted that, in the absence of a reference standard (vitrectomy not being accepted as a reference standard), it was not possible to know whether OCT is detecting more true positives or more false positives. Ideally, this question would be addressed by comparing the natural history of the additional detected cases with that of the other cases. Overall, the natural history of VMT was unclear and therefore the additional cases identified might represent a less severe manifestation of disease with a slower rate of progression or a greater likelihood of spontaneous resolution. As an indication of this variable natural history, MSAC noted that:

- very mild VMT can spontaneously resolve in 32% of patients (John, 2014)
- 50-75% of patients with MH progress over 1-2 years (Hikichi, 1995; Kim, 1996; Kishi, 2000)
- full thickness MH can spontaneously close in 3-11% (Syed, 2013).

A cost-utility analysis comparing OCT with ocriplasmin with and without vitrectomy versus OCT with watchful waiting with and without vitrectomy was performed. The model estimates the costs and consequences for 3 subgroups of VMT patients:

- VMT only
- VMT with ERM, but no MH
- VMT with MH, with or without ERM.

MSAC was concerned that the economic model included OCT in both of its arms, thus making it impossible to ascertain the added value of using OCT compared with not using OCT, especially in relation to any consequences for changing the proportions of false positive and false negative results.

MSAC understood that, despite an attempt in the pre-ESC response to address the question of the added value of using OCT via sensitivity analyses of the economic model, there was no data to inform the counterfactual of treating with ocriplasmin without prior OCT. In addition, any ability of OCT results to predict any variation in the effectiveness of ocriplasmin would be difficult to distil from the rest of the diagnostic work-up of eligible patients. Given the absence of such data, MSAC noted the importance of assessing the best evidence available of test performance in terms of analytical validity and clinical validity to support the clinical utility claim based on using OCT in both arms of the ocriplasmin trials.

OCT costs were a relatively minor component of the co-dependent package, with two OCTs equating to approximately **(redacted)**% of the cost of ocriplasmin at $**(redacted)** per eye per patient lifetime. However, the estimated costs to the MBS for OCT scans (less than $500,000 per annum) are likely to be underestimated, particularly because of the incentive to adopt a likely broad interpretation of suspected VMT to justify billing the OCT service to the MBS even when other ocular conditions may be more likely. This risk of use beyond the intention of the item descriptor might be reduced by extending the description of "suspected disease" to include text along the lines of "symptoms suggestive of VMT". The costs to the MBS for administering ocriplasmin in the eye (less than $500,000) would vary to the extent that utilisation of ocriplasmin varies from the estimates for the PBS.

4. Background

Assessment of OCT for treatment of VMT with or without full thickness macular hole (FTMH) has not been previously assessed by MSAC.

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 did not support public funding of OCT with respect to these indications due to insufficient evidence to support the clinical claims.

At its 5 April 2013 meeting, MSAC discussed Application 1350, a referral from the November 2012 PBAC meeting for advice on any co-dependency between OCT and ranibizumab in managing retinal vein occlusion (RVO).

At its 1 August 2013 meeting, MSAC considered MBS listing of 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) (Application 1310). MSAC did not 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.

5. Prerequisites to implementation of any funding advice

OCT devices for retinal and macular imaging are listed on the Australian Register of Therapeutic Goods.

6. Proposal for public funding

The application proposed MBS listing for OCT was:

(i) to confirm VMT diagnosis and determine patient eligibility for treatment with ocriplasmin (at least one OCT); and
(ii) to assess treatment response (one OCT).

The proposed fee is based on the current DVA fee.

Applicant proposed MBS item descriptors for OCT for the determination of eligibility and efficacy assessment of treatment with ocriplasmin

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
MBS ####   Optical coherence tomography by an ophthalmologist to determine if the requirements relating to vitreomacular traction including those associated with full thickness macular hole for access to ocriplasmin under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.   Fee: $91.75   Explanatory notes   Suspected diagnosis of VMT with (or without) FTMH using baseline standard ophthalmic assessment (including biomicroscopy) by professional attendance of an ophthalmologist is required.
MBS ####   Optical coherence tomography by an ophthalmologist for the assessment of patient response to PBS-subsidised ocriplasmin, claimable only once per eye per lifetime.   Fee: $91.75   Explanatory notes   Single OCT assessment after one injection of ocriplasmin

The proposed item descriptors are consistent with the descriptors agreed in the DAP.

The intention of the proposed MBS and PBS listings of OCT/ocriplasmin is that all suspected VMT patients will receive (at least) one OCT procedure at baseline and all treated patients will receive one further OCT procedure at follow-up.

7. Summary of Public Consultation Feedback/Consumer Issues

Consumer input reflected that any deterioration of visual function causes great stress, not only because of the causative disease, but also because of the consequences of investigations and treatments to the eye. There is therefore a preference for better and less invasive investigations and treatments. Although watchful waiting may be a viable strategy, the common perception is that the clinician does the watching and the patient does the waiting, which reduces visibility and the autonomy of the patient, as well as raising concerns about equity of access and waiting times when a treatment is indicated. In relation to costs, the addition of additional investigations as a new routine can escalate out-of-pocket costs to the consumer as well as costs to the government, so consumers seek reassurance that these investigations are worthwhile.

8. Proposed intervention's place in clinical management

The algorithms presented in the submission indicate that publically funded OCT would replace privately funded OCT to confirm VMT diagnosis in "suspected" VMT patients. OCT is proposed to be used in the diagnosis of VMT ± MH and assessment of eligibility for, and outcome following, treatment with ocriplasmin, thus two OCT examinations per patient are expected. OCT would be used in addition to the currently available tests.

9. Comparator

The submission nominated standard ophthalmic assessment without OCT as the main comparator for OCT plus standard ophthalmic assessment. That is, OCT will be complementary to standard ophthalmic assessment, which includes but is not limited to slit lamp biomicroscopy and clinical observations.

Standard assessment is included in the MBS fee structure for professional attendance – comprehensive consultation (MBS item 104).

10. Comparative safety

The implications for treating false positives with ocriplasmin are unknown. False positives could be at risk of experiencing any adverse events associated with ocriplasmin, but the potential for further risks cannot be quantified. The implications for not treating false negative patients could be deterioration of visual acuity and the potential to progress the condition to a macular hole, however based on the available data presented above, OCT consistently detected the same number or more cases, thus this is unlikely.

There are no differences in the comparative safety of the test strategies as OCT is a noninvasive, non-contact test that will be used in addition to a number of other tests.

11. Comparative effectiveness

The comparative analytical performance of OCT was determined versus intra-operative findings (two studies) and biomicroscopy, with or without other clinical investigations (13 studies).

Two test-retest studies (Benson, 2008, N=47; and DeCroos, 2012, N=100) were provided to assess analytical validity for estimating the size of a macular hole. The results suggest no systematic or statistically significant differences, but wide scatter (e.g. DeCroos, 2012 reported mean (SD) paired difference in minimum width of FTMH was 34.4 (93.8) micrometres between initial and repeat grading, which suggests a 95% CI of ± 180 micrometres). Similarly, kappa statistics for inter-observer agreement of the diagnosis of VMT (0.91, 95% CI: 0.81, 1.0) or MH (0.87, 95% CI: 0.78, 0.95) reported by DeCroos, 2012 (N=100) were high and consistent with Folgar, 2012 (N=186) and Liu, 2011 (N=193). However, the ability of OCT to differentially diagnose between macular pseudoholes or lamellar macular holes from FTMH associated with VMT was less strongly supported, with Hee, 1995 (N=50) and Bottos, 2012 (N=29) suggesting that OCT might be a better discriminator than retinal photo.

Two studies comparing OCT with intraoperative findings were provided to assess clinical validity. The reliability of intraoperative findings for the diagnosis of VMT ± MH indication is not known. One study (Rahman, 2012, N=50) suggested that OCT has a high sensitivity and specificity for determining VMT diagnoses compared with intraoperative observation with a high kappa statistic of 0.947. The other study (Kikova, 2012, N=30) suggested otherwise, with findings that only one of eight OCT determinations were correct according to intraoperative findings. This study was considered to be a likely outlier.

Thirteen studies compared OCT with biomicroscopy, with or without other clinical investigations, which represents an assessment of analytical concordance. The table below summarises the results from these studies in the detection of VMT/posterior vitreous

detachment (PVD), MH or ERM, and thus whether OCT detected more (OCT>BIOM), the same number (OCT=BIOM) or fewer (OCT<BIOM) cases compared with biomicroscopy, with or without other clinical investigations.

Summary of the studies comparing OCT and biomicroscopy, with or without other clinical investigations in detecting VMT/PVD, MH or ERM

	VMT/PVD	MH	ERM
OCT>BIOM	k=2, n=286	k=3; n=170	k=1; n=84
OCT=BIOM	k=1; n=61	k=2; n=78	k=1, n=70
OCT<BIOM, compared with intraoperative findings	k=1; n=30[a]	-	-

[a] study reported issues with clarity of OCT images

k=studies, n=eyes

One study provided data for detecting VMT/PVD and ERM, both demonstrating OCT>BIOM

Three further studies reported that OCT provided different information to biomicroscopy, with or without other clinical investigations in detecting VMT/PVD (one study) and MH (two studies).

Overall, there is an indication that OCT is more sensitive or provides additional information with respect to diagnosing or staging VMT, MH or ERM compared with biomicroscopy, with or without other clinical investigations.

Two trials excluded patients with a macular hole greater than 400µm, so there is no direct evidence to determine whether ocriplasmin is less effective in patients with larger macular holes. There is indirect evidence from Gupta, 2009 (N=133), which reported that the odds ratio of visual success following vitrectomy reduced significantly as the hole size increased above 350µm.

12. Economic evaluation

The application presented a cost-utility analysis comparing OCT with ocriplasmin with and without vitrectomy versus OCT with watchful waiting with and without vitrectomy.

13. Financial/budgetary impacts

MSAC agreed with the ESC proposal that consideration be given to benchmarking the fee for the proposed item for the OCT assessment after ocriplasmin to $54.55 with reference to MBS Item 55005 (i.e. an ultrasound scan of the orbit as a type of an ultrasound scan of the head).

Assuming each patient receives two OCTs (pre-/post-injection), then the total OCT costs would be $183.50 per course of treatment ($91.75 x 2; MT12 under the DVA benefits). The cost to the MBS for OCT scans was estimated to be less than $1 million per year.

The combined PBS/MBS costs (i.e., ocriplasmin, OCT, intravitreal injections) are estimated to be between $10 – $30 million in Year 5.

14. Key issues from ESC for MSAC

Clinical issues

- The natural history of VMT is not clear, so the possibility of natural resolution or differential rates of progression are unknown.
- Without this information, it is difficult to distinguish between an increase in diagnostic yield with OCT and an over sensitive detection of patients for treatment.

- Whether the submission has adequately addressed the consequences of limiting OCT to confirming the diagnosis and selection of patients with VMT ± MH for ocriplasmin treatment.

Economic issues

- The model presented in the submission assumed that OCT would be used in both arms of the comparison, so there was no basis to assess how OCT might affect the effectiveness and cost-effectiveness of any therapy. Although the pre-Sub-Committee response (PSCR) attempted to address these questions through "simple adaptions" of the base model, this involved only one of the three subgroups (VMT only) and resulted in developing a whole new model. The ESCs considered that the approach provided a weak basis for MSAC consideration.
- The approach also did not consider the possibility that OCT might result in false positive and false negative results.
- Concerns with the main model for ocriplasmin affect the further modifications required to address these questions and the main model would need to be acceptable before making these modifications.

Financial issues

The estimated OCT numbers are considered an underestimate, for the following three reasons.

1) The estimates are only for those who will be treated with ocriplasmin and do not account for those:

- with a suspected diagnosis of VMT ± MH who have a subsequent diagnosis of no VMT ± MH;
- with a suspected diagnosis of VMT ± MH who have a subsequent diagnosis of VMT ± MH and meet the eligibility criteria of MH size ≤400μm, but opt not to have ocriplasmin treatment;
- with a suspected diagnosis of VMT ± MH who have a subsequent diagnosis of VMT ± MH, but do not meet the eligibility criteria for ocriplasmin (i.e., MH size >400μm) or those
- who have other retinal pathology that could be detected using OCT, i.e. "usage beyond the applicant's intent with the item descriptor".

Therefore the number of initial OCTs is likely to be an underestimate.

2) The requested OCT restriction does not restrict the number of initial OCTs to 1 per suspected patient. Therefore, patients with suspected VMT may receive more than one "initial" OCT should no diagnosis be made and should VMT be suspected again in the future or should a confirmatory OCT be conducted if ocriplasmin is not administered in the same consultation as the diagnostic OCT.

3) As the estimated number of patients treated with ocriplasmin is a likely underestimate, the number of follow-up OCTs is also likely to be an underestimate.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

Alcon are pleased that the MSAC support an expedited process for MBS listing of OCT to ensure public funding of OCT is aligned with the circumstances recommended by the PBAC for ocriplasmin. Alcon will continue to work with the PBAC to ensure ocriplasmin is made available on the PBS for eligible Australian patients.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.