

7.07 OCRIPLASMIN
intravitreal injection, 0.5 mg/2 mL,
Jetrea®, Alcon.

1 Purpose of Application

1.1 Authority Required listing for ocriplasmin for treatment of vitreomacular traction (VMT) excluding patients with epiretinal membrane (ERM) or adhesion diameter >1500 µm. The first and only previous submission was an integrated co-dependent submission considered in November 2014.

2 Requested listing

2.1 The requested PBS listing is presented below.

2.2 The basis for the requested listing was a cost-utility analysis comparing ocriplasmin (±vitrectomy) to watchful waiting (±vitrectomy).

2.3 Five new clinical criteria were added to the requested restriction. The first two additional criteria exclude patients with (i) an adhesion diameter >1500 µm and/or (ii) an epiretinal membrane, which the re-submission argued were negative treatment effect modifiers. The three other additional criteria were designed to align the requested restriction with the inclusion/exclusion criteria of the trial evidence.

2.4 The requested effective price (DPMQ) was reduced from \$ [REDACTED] to \$ [REDACTED] under a proposed special pricing arrangement with a published price of \$ [REDACTED].

2.5 The PSCR stated that PBAC may wish to consider excluding patients with a macular hole. The ESC considered that the data weakly suggested that patients with an established macular hole would be more likely to go on to require surgery regardless of treatment with ocriplasmin.

2.6 The ESC noted the clinical criteria proposed in the re-submission: “Patient must be symptomatic with severe/intolerable symptoms”. The ESC was concerned that symptoms were not defined and may be difficult to assess and that OCT may be used for screening rather than diagnostic purposes in practice. The ESC considered that the Secretariat-suggested criteria of “Patient must be symptomatic” as appropriate.

2.7 The presence of ERM was part of the exclusion criteria of the OASIS trial, but the ESC noted that patients with ERM were recruited into this trial. The ESC was concerned that even with the inclusion of clinical criteria ‘Patient must not have an epiretinal membrane (ERM) attached to the vitreomacular traction (VMT)’, there remains a risk of leakage of treatment of patients with ERM.

2.8 Suggestions and additions by the Secretariat are in *italics* and deletions are in ~~strikethrough~~.

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| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|---|----------|-------------|------------------------------|-----------------------------------|
| OCRIPLASMIN 0.5 mg/ 0.2 mL injection, 1x 0.2 mL vial | 1 | 0 | \$ [REDACTED] | Jetrea Alcon |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Episodicity: | - |
| Severity: | - |
| Condition: | Vitreomacular traction syndrome including those with FTMH |
| PBS Indication: | Vitreomacular traction syndrome including those with FTMH |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Treatment criteria: | Must be treated by an ophthalmologist |
| Clinical criteria: | The condition must be confirmed by ocular coherence tomography AND The condition must have an vitreomacular adhesion diameter less than or equal to 1500 micrometres as determined by ocular coherence tomography μm (as determined by OCT) AND Patient must not have an epiretinal membrane (ERM) attached to the vitreomacular traction (VMT) AND The patient must have visual impairment due to vitreomacular traction (VMT) without a full thickness macular hole (FTMH) OR The patient must have visual impairment due to vitreomacular traction (VMT) with a full thickness macular hole (FTMH) of a diameter of less than or equal to 400 micrometres as determined by ocular coherence tomography AND The macular hole, if applicable, must have traction present and be of a diameter $\leq 400 \mu\text{m}$ (as determined by OCT) AND The condition must be previously untreated in the eye proposed for treatment Patient must not have received prior treatment with ocriplasmin in the same eye AND Patient must not have received prior vitrectomy in the eye proposed for treatment in the same eye AND Patient must be symptomatic with severe/intolerable symptoms AND Patient must have documented visual impairment defined as a best corrected visual acuity score of approximate Snellen equivalent 20/25 or worse in the eye proposed for treatment Patient must have a baseline BCVA of 20/25 or worse in the study eye |

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| | |
|---------------------------------------|--|
| <p>Prescriber Instructions</p> | <p><i>The authority application for each eye must be made in writing or by telephone.</i></p> <p><i>A written application must include:</i></p> <p><i>a) a completed authority prescription form;</i></p> <p><i>b) a completed [name to be determined] - PBS Supporting Information Form; and</i></p> <p><i>c) a copy of the optical coherence tomography (OCT) report.</i></p> <p><i>A telephone application must be made following submission by facsimile of a copy of a completed [name to be determined] - PBS Supporting Information Form and a copy of the OCT report. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised.</i></p> |
| <p>Administrative Advice</p> | <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 HOBART TAS 7001</i></p> <p><i>The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p> |

For more detail on PBAC's view, see section 7 "PBAC outcome".

3 Background

- 3.1 TGA status: Ocriplasmin was TGA registered on 2/11/2015 for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns.
- 3.2 The PBAC and MSAC previously considered ocriplasmin and ocular coherence tomography (OCT) based on an integrated co-dependent submission (MSAC application no.1370) in November 2014. The PBAC rejected the submission for ocriplasmin on the basis of that cost-effectiveness of ocriplasmin is highly uncertain because it remains unclear how effective ocriplasmin is with regard to the patient-relevant outcomes of improving visual function and of preventing rather than delaying vitrectomy in the long-term, and considered the modelled evaluation did not provide a suitable basis for decision-making. MSAC deferred the application for OCT until such time as the 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 treatment of VMT, then MSAC would support an expedited process of reconsideration. A coordinated co-dependent submission has been lodged for the 31 March, 1 April 2016 MSAC meeting.

3.3 A summary of the previous and current submissions is presented below.

Summary of the previous and current submissions

| | Ocriplasmin November 2014 | Current submission |
|------------------------|---|---|
| Requested PBS listing | <ul style="list-style-type: none"> Vitreomacular traction (VMT) including those with macular hole. <p>PBAC Comment: The PBAC noted the requested restriction was consistent with the populations in the trials however some exclusion criteria (visual acuity and comorbidities such as AMD) were not included (Paragraph 7.2).</p> | <ul style="list-style-type: none"> Vitreomacular traction (VMT) including those with macular hole, excluding epiretinal membrane (ERM), adhesion diameter >1500µm, BCVA better than 20/25. |
| Requested price | <ul style="list-style-type: none"> Requested DPMQ = \$ [REDACTED]. | <ul style="list-style-type: none"> Requested DPMQ = \$ [REDACTED], effective price = \$ [REDACTED]. |
| Main comparator | <ul style="list-style-type: none"> Watchful waiting ± vitrectomy. <p>PBAC Comment: The PBAC considered the comparator appropriate (Paragraphs 5.2 and 7.4).</p> | <ul style="list-style-type: none"> Watchful waiting ± vitrectomy. |
| Clinical evidence | <ul style="list-style-type: none"> Two RCTs: TG-MV-006 (N=326) and TG-MV-007 (N=326). <p>PBAC Comment: The risk of bias was low and patients enrolled were considered to be broadly representative of those for whom listing is sought (Paragraph 6.6).</p> | <ul style="list-style-type: none"> Three RCTs: TG-MV-006 (N=326), TG-MV-007 (N=326) and OASIS (n=220). |
| Key effectiveness data | <ul style="list-style-type: none"> Non-surgical VMT resolution at Day 28 favoured ocriplasmin (RD=0.17, 95% CI: 0.12, 0.23); there was a small change in patient-relevant secondary outcome of vitrectomy at 6 months (RD=-0.08, 95% CI: -0.16, -0.01) but no change in BCVA at 6 months (Mean difference=1.11, 95% CI: -0.64, 2.85). <p>PBAC Comment: The PBAC noted the primary outcome may be a reasonable surrogate for patient relevant outcomes of visual acuity, visual disturbance and vitrectomy, however the potential relationship was not presented. The PBAC also noted that successful non-surgical VMT resolution at Day 28 did not appear to reliably predict avoidance of vitrectomy at 6 months. Overall, the PBAC considered it remained unclear how effective ocriplasmin is with respect to the patient relevant outcomes of improving visual function and of preventing rather than delaying vitrectomy (Paragraphs 7.5 and 7.6).</p> | <ul style="list-style-type: none"> Non-surgical VMT resolution at Day 28 (RD=0.23, 95% CI: 0.11, 0.35). No difference in vitrectomy at 6 months (RD=-0.09, 95% CI: -0.23, 0.04) or at 24 months (RD=-0.11, 95% CI: -0.24, 0.03). No difference in change in BCVA at 6 months (mean difference =1.32, 95% CI: -0.20, 2.84) or at 24 months (mean difference=2.30, 95% CI: -0.85, 5.45). |
| Key safety data | <ul style="list-style-type: none"> No safety concerns. <p>PBAC Comment: None.</p> | <ul style="list-style-type: none"> No new safety concerns. |
| Clinical claim | <ul style="list-style-type: none"> Ocriplasmin superior effectiveness compared with watchful waiting, but inferior safety. <p>PBAC Comment: The PBAC accepted this claim (Paragraph 7.8) but noted there was no claim for ocriplasmin ± vitrectomy vs watchful waiting ± vitrectomy (Paragraph 6.28).</p> | <ul style="list-style-type: none"> Ocriplasmin ± vitrectomy superior effectiveness compared with watchful waiting ± vitrectomy, but inferior safety. |
| Economic evaluation | <ul style="list-style-type: none"> Cost-utility model with cost/QALY over [REDACTED] years: \$15,000/QALY - \$45,000/QALY in VMT only subgroup; \$45,000/QALY - \$75,000/QALY in VMT+ERM subgroup; \$15,000/QALY - \$45,000/QALY in VMT+MH subgroup; weighted=\$15,000/QALY - \$45,000/QALY <p>PBAC Comment: The PBAC considered the ICER was not informative because of model concerns:(i) the clinical value of ocriplasmin was not clear, (ii) the justification of the subgroups was unclear and differed to those pre-specified in the trials, (iii) the structure of the model was overly complex, (iv) the transitions unable to be assessed due to paucity of data, and (v) source of utilities is inappropriate (Paragraphs 7.8, 7.9 and 7.10)</p> | <ul style="list-style-type: none"> Cost-utility model with cost/QALY over [REDACTED] years: \$15,000/QALY - \$45,000/QALY (ITT OASIS). |
| Number of patients | <ul style="list-style-type: none"> Treated patients: less than 10,000 per year in Year 1 increasing to less than 10,000 per year in Year 5. <p>PBAC Comment: The PBAC considered the estimates were unreliable (Paragraph 7.11).</p> | <ul style="list-style-type: none"> Treated patients: Less than 10,000 per year in Year 1 increasing to less than 10,000 per year in Year 5 (excluding patients with ERM or adhesion diameter >1500 µm). |

| | Ocriplasmin November 2014 | Current submission |
|----------------------------|--|---|
| Estimated cost to PBS/RPBS | <ul style="list-style-type: none"> Less than \$10 million in Year 1 increasing to in Year 5 for a total of \$30 - \$60 million over the first 5 years of listing. <p>PBAC Comment: The PBAC considered the estimates were unreliable (Paragraph 7.11).</p> | <ul style="list-style-type: none"> Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$20 - \$30 million over the first 5 years of listing. |
| PBAC decision | <ul style="list-style-type: none"> Reject. On the basis that cost-effectiveness is highly uncertain because it remains unclear how effective ocriplasmin is with regard to the patient-relevant outcomes of improving visual function and of preventing rather than delaying vitrectomy in the long-term, and the modelled evaluation did not provide a suitable basis for decision making (Paragraph 7.1). | |

Source: Compiled during the evaluation

4 Clinical place for the proposed therapy

- 4.1 Vitreomacular traction (VMT) is an uncommon condition which is symptomatic and progressive and predominantly affects older people. VMT can be associated with a macular hole (MH) and/or an epiretinal membrane (ERM). There is currently one active treatment available to treat these patients (surgical vitrectomy). As VMT can resolve spontaneously, patients may undergo a period of watchful waiting before vitrectomy. The proposed ocriplasmin listing is intended to provide another alternative prior to vitrectomy. If ocriplasmin is unsuccessful, patients would then be treated with vitrectomy.
- 4.2 The re-submission's proposed place in therapy is unchanged from the integrated co-dependent submission.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 The comparison was best described as ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy. This is the appropriate comparator and is unchanged from the integrated co-dependent submission.

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease, particularly in outlining the nature of visual disturbances associated with VMT which are not assessed by visual acuity but which can affect quality of life. The PBAC noted that, in clinical practice, prior

treatment with ocirplasmin would not likely impact on the outcome for a patient receiving a vitrectomy at later date.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The re-submission was based on three head-to-head trials comparing ocirplasmin ± vitrectomy to watchful waiting ± vitrectomy (N=872). The re-submission included one additional trial not previously considered by the PBAC: OASIS.

6.4 Details of the trials presented in the re-submission are provided in Table 1.

Table 1: Trials and associated reports presented in the re-submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|------------------------------------|--|--|
| Direct randomised trials | | |
| TG-MV-006 (NCT00781859) | Clinical Study Report. Ocirplasmin. TG-MV-006. A randomised, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non-surgical treatment of focal vitreomacular adhesion. | ThromboGenics, 27 Jun 2011 |
| | Stalmans P, Benz M S, Gandorfer A, Kampik A, Girach A, Pakola S, Haller J A. Enzymatic vitreolysis with ocirplasmin for vitreomacular traction and macular holes. | New England Journal of Medicine 2012, 367(7):606-615 |
| TG-MV-007 (NCT00798317) | Clinical Study Report. Ocirplasmin. TG-MV-007. A randomised, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non-surgical treatment of focal vitreomacular adhesion. | ThromboGenics, 27 Jun 2011 |
| | Stalmans P, Benz M S, Gandorfer A, Kampik A, Girach A, Pakola S, Haller J A. Enzymatic vitreolysis with ocirplasmin for vitreomacular traction and macular holes. | New England Journal of Medicine 2012, 367(7):606-615 |
| OASIS / TG-MV-014 (NCT01429441) | Clinical Study Report. TG-MV-014. A randomised, sham-controlled double-masked, multicentre study evaluating ocirplasmin treatment for symptomatic vitreomacular adhesion (VMT) including macular hole. | ThromboGenics, 28 August 2015 (Draft 3) |

Source: Tables 16 and 17, pp64-65 of the re-submission

6.5 The key features of the direct randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

| Trial | N | Design/ duration | Bias | Patient population | Key outcomes | Use in model |
|-----------|-----|--------------------------------|------------------|------------------------------------|---|--------------|
| TG-MV-006 | 326 | R, DB, PC, MC / 6 mths | Low | ≥18years; VMT±MH; OCT confirmed | Non-surgical VMA resolution; FTMH closure; Vitrectomy; BCVA; VFQ-25 | No |
| TG-MV-007 | 326 | | | | | |
| OASIS | 220 | R, DB, SC, MC, CO / 24 mths | Low ^a | ≥18years; VMT±MH; OCT confirmed | Non-surgical VMA resolution; FTMH closure; Vitrectomy; BCVA; VFQ-25 | Yes |

DB=double blind; MC=multi-centre; R=randomised; PC=placebo-controlled; SC=sham-controlled; CO=cross-over; VMA / VMT=vitreomacular adhesion / traction; MH=macular hole; FTMH=full thickness macular hole; BCVA=best corrected visual acuity; VFQ-25=25-item Visual Function Questionnaire; OCT=optical coherence tomography

^a Although the injecting physician was not blinded, the trial is considered low risk of bias due to an identical injecting procedure ensuring the patient and investigators remained blinded.

Source: compiled during the evaluation

- 6.6 All trials compared a single intravitreal injection of ocriplasmin 125 µg with intravitreal placebo (TMG-MV-006 and TG-MV-007) or sham (OASIS) injection in subjects with symptomatic VMA/VMT including macular hole. Trials TG-MV-006 and TG-MV-007 were identical with respect to trial design, treatment regimen and outcomes. The trial protocols of TG-MV-006, TG-MV-007 and OASIS permitted vitrectomy at any point after 28 days (or 1 month) if the patients did not achieve VMA resolution, or at any point after day 1 if BCVA worsened by >2 lines (or 10 letters). Patients in OASIS were also permitted to cross-over at any time during the trial if vitrectomy was deemed necessary, or at any time after 12 months. Approximately █% of subjects initially randomised to the sham injection crossed over to receive ocriplasmin compared with approximately █% of subjects randomised to ocriplasmin. The ESC noted that there was no analysis of this cross-over, but that relying on the ITT/FAS analyses of the results would be conservative.
- 6.7 The ESC noted that:
- Compared with the OASIS trial, which used a sham procedure comparator, the incremental effect of ocriplasmin in the TMG-MV-006 and TG-MV-007 trials was possibly different, due to the use of a placebo injection. However, comparator response rates for the primary outcome were similar across the three trials (particularly across OASIS and TG-MV-007).
 - The investigators who performed the injections were not involved in subsequent management to ensure that trial participants and other investigators who subsequently managed the participants did not know whether the injection included ocriplasmin or not.
 - It was not possible to determine whether those randomised to the comparator who crossed over to ocriplasmin were less likely to require vitrectomy.

Comparative effectiveness

- 6.8 Tables 3 and 4 summarise the primary outcome of the trials, non-surgical VMA resolution at Day 28, and patient relevant secondary outcomes of vitrectomy at 6 and 24 months, and improvement in BCVA at 6 and 24 months. The results indicated that any statistically significant differences in patient relevant secondary outcomes observed at 6 months were no longer observed by 24 months.

Table 3: Results of primary outcome (VMA resolution at Day 28) and patient-relevant secondary outcomes (vitrectomy and ≥ 3 lines improvement in BCVA) across the direct randomised trials

| Trial ID | Ocriplasmin n/N (%) | Control n/N (%) | RD (95% CI) | RR (95% CI) | NNT (95% CI) |
|---|------------------------|--------------------|---------------------|--------------------|--------------|
| Non-surgical VMA resolution without creation of an anatomical defect at Day 28 (FAS) | | | | | |
| TG-MV-006 | 61/219 (27.9) | 14/107 (13.1) | 0.15 (0.06, 0.23) | 2.13 (1.25, 3.63) | 7 (4, 17) |
| TG-MV-007 | 62/245 (25.3) | 5/81 (6.2) | 0.19 (0.12, 0.27) | 4.10 (1.71, 9.84) | 5 (4, 8) |
| OASIS | | | | | |
| Pooled | | | | | |
| Vitrectomy required (FAS) | | | | | |
| Month 6 | | | | | |
| TG-MV-006 | 45/219 (20.5) | 31/107 (29.0) | -0.08 (-0.19, 0.02) | 0.71 (0.48, 1.05) | NA |
| TG-MV-007 | 37/245 (15.1) | 19/81 (23.5) | -0.08 (-0.19, 0.02) | 0.64 (0.39, 1.05) | NA |
| OASIS | | | | | NA |
| Pooled | | | | | NA |
| Month 24 | | | | | |
| OASIS | 48 | | | | NA |
| ≥ 3 lines improvement in best corrected visual acuity (BCVA) (FAS) | | | | | |
| Month 6 | | | | | |
| TG-MV-006 | 28/219 (12.8) | 9/107 (8.4) | 0.04 (-0.02, 0.11) | 1.52 (0.74, 3.11) | NA |
| TG-MV-007 | 29/245 (11.8) | 3/81 (3.8) | 0.08 (0.02, 0.14) | 3.20 (1.00, 10.21) | 13 (7, 50) |
| OASIS | | | | | NA |
| Pooled | | | | | |
| Month 24 | | | | | |
| OASIS | | | | | NA |

Source: Tables 31 to 35, pp102-117 of the re-submission

Table 4: Results of patient-relevant secondary outcome mean improvement in BCVA letters from baseline across the direct randomised trials (FAS)

| Trial | Ocriplasmin n/N (%): mean (SD) | Control n/N (%): mean (SD) | Mean difference (95%CI) |
|------------------|-----------------------------------|-------------------------------|----------------------------|
| 6 months | | | |
| TG-MV-006 | 219/219 (100%) 3.5 (12.30) | 107/107 (100%) 2.8 (9.89) | 0.70 (-1.78, 3.18) |
| TG-MV-007 | 245/245 (100%) 3.6 (10.35) | 80/81 (98.77%) 2.1 (9.49) | 1.50 (-0.95, 3.95) |
| OASIS | | | |
| Pooled | | | |
| 24 months | | | |
| OASIS | | | |

Source: Tables 36 and 37, pp121-122 of the re-submission

- 6.9 The re-submission also presented two relevant *post hoc* outcomes “no anatomical abnormalities without vitrectomy” and “no anatomical abnormalities regardless of vitrectomy” from TG-MV-006 and GT-MV-007 at 6 months. The results indicated statistically significantly fewer patients treated with ocriplasmin had an anatomical abnormality without vitrectomy, but there was no difference after accounting for vitrectomy.
- 6.10 The ESC noted that, in the OASIS trial, non-surgical VMA resolution without creation of an anatomical defect by visit at Month 24 was significantly different (RD ██████);

95% CI: [redacted], [redacted]) in the ocriplasmin arm ([redacted]/[redacted] ([redacted]%) compared to the sham control ([redacted] ([redacted]%). Further, the PSCR (p1 and 5 and Figure 1) presented a meta-analysis on no anatomical abnormality regardless of vitrectomy in the ITT population (see also Table 5 below).

Table 5: No anatomical abnormality regardless of vitrectomy (ITT)

| Trial | Ocriplasmin n/N (%) | Control n/N (%) | RD (95% CI) | NNT (95% CI) | RR (95% CI) |
|---------------------|------------------------|--------------------|--------------------|-----------------|-------------------|
| At 6 months | | | | | |
| TG-MV-006 | 90/219 (41.1) | 37/107 (34.6) | 0.07 (-0.05, 0.18) | NE | 1.19 (0.88, 1.61) |
| TG-MV-007 | 88/245 (35.9) | 23/81 (28.4) | 0.08 (-0.04, 0.19) | NE | 1.26 (0.86, 1.86) |
| OASIS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pooled | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| At 24 months | | | | | |
| OASIS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

- 6.11 The 25-item Visual Function Questionnaire (VFQ-24) measured the Quality of Life of patients during the presented trials. Table 6 presents the mean change in VFQ-25 composite score from baseline to 6 months in the trials. The VFQ-25 scores range between 0 (worst possible) and 100 (best possible). Although this was not a pre-specified outcome in OASIS, the results were extracted during the evaluation and presented below.

Table 6: Mean change from baseline to 6 months in VFQ-25 composite score (FAS)

| | | Ocriclasmin | | | Placebo | | | Mean difference (95%CI) | Pooled mean difference at 6 months (95%CI) | |
|-----------|-----------|-------------|--------------|-----------------------|---------|--------------|------------------------|-------------------------|--|-------------------|
| | | N | Value | Diff. (SD) | N | Value | Diff. (SD) | | | |
| TG-MV-006 | Baseline | 218 | 78.8 (15.02) | (N=198) 3.5(11.74) | 107 | 83.0 (11.56) | (N=99) 1.2 (9.86) | 2.30 (-0.24,4.84) | 2.79 (0.91, 4.68) | 2.97 (1.21, 4.74) |
| | 6 months | 199 | 82.3 (15.88) | | 99 | 84.3 (11.93) | | | | |
| TG-MV-007 | Baseline | 244 | 75.6(16.54) | (N=230) 3.3(11.97) | 80 | 80.6(12.85) | (N=74) -0.1 (10.29) | 3.40 (0.59,6.21) | | |
| | 6 months | 231 | 78.9(16.65) | | 75 | 80.3(15.49) | | | | |
| OASIS | Baseline | ■ | ■ | Ref. | 26 | ■ | Ref. | ■ | | |
| | 6 months | ■ | ■ | ■ | 26 | ■ | ■ | ■ | | |
| | 12 months | ■ | ■ | ■ | 26 | ■ | ■ | ■ | | |
| | 24 months | ■ | ■ | ■ | 26 | ■ | ■ | ■ | | |

Source: Table 38, p125 of the re-submission; Table 10.9.1, p3276 OASIS CSR

- 6.12 The re-submission stated that the minimum clinically important difference in the VFQ-25 composite score is 3.6 points. Based on either the pooled results across TG-MV-006 and TG-MV-007 or all three trials, the weighted mean difference was statistically significant in favour of ocriclasmin to 6 months, but did not reach the minimum clinically important difference proposed by the re-submission.
- 6.13 Table 7 presents the proportion of patients who achieved ≥ 5 point improvement in the VFQ-25 composite score from baseline to 24 months in OASIS. Significantly more patients treated with ocriclasmin achieved this outcome.

Table 7: Proportion ≥ 5 -point improvement in VFQ-25 composite score from baseline at 24 months, irrespective of vitrectomy (FAS)

| Trial | Ocriclasmin n/N (%) | Control n/N (%) | RD (95% CI) | NNT (95% CI) | RR (95% CI) |
|-------|---------------------|-----------------|-------------|--------------|-------------|
| OASIS | ■ | ■ | ■ | ■ | ■ |

Source: Table 29, p100 of the OASIS CSR
NNT were calculated during the evaluation by (1/RD)

- 6.14 The ESC noted these patient-relevant outcomes, but also noted that there were issues with these results, for example, the trials did not consistently adjust for differences in the baseline VFQ-25 scores across treatment arms, and the dichotomised results in Table 7 need to be considered in the context of there being no clinically important differences across the mean changes from baseline in VFQ-25 (the prespecified metric of reporting the VFQ-25 for the purposes of determining the minimal clinically important difference).

Comparative harms

- 6.15 A summary of adverse events reported in the trials are provided in Table 8. All drug-related adverse events were ocular in nature with the most common being vitreous

floaters, eye pain, photopsia, blurred vision/impairment and conjunctival haemorrhage post-injection. The majority of adverse events occurred within the first week post-injection, were non-serious and mild in intensity and resolved within 2-3 weeks. In OASIS, chromatopsia and abnormal colour vision tests were also commonly reported by patients randomised to ocriplasmin.

Table 8: Summary of adverse events in the randomised trials (SAS)

| | TG-MV-006 | | TG-MV-007 | | OASIS | |
|------------------|----------------------------|------------------------|----------------------------|-----------------------|----------------------------|--------------------|
| | Ocriplasmin n/N (N=220) | Placebo n/N (N=106) | Ocriplasmin n/N (N=245) | Placebo n/N (N=81) | Ocriplasmin n/N (N=146) | Sham n/N (N=74) |
| All AEs | 182 (82.7) | 77 (72.6) | 176 (71.8) | 52 (64.2) | | |
| Ocular | 163 (74.1) | 65 (61.3) | 162 (66.1) | 42 (51.9) | | |
| SE | 159 (72.3) | 62 (58.5) | 159 (64.9) | 38 (46.9) | | |
| Drug-related AEs | 93 (42.3) | 21 (19.8) | 93 (38.0) | 19 (23.5) | | |
| Ocular | 93 (42.3) | 21 (19.8) | 93 (38.0) | 19 (23.5) | | |
| SE | 93 (42.3) | 21 (19.8) | 93 (38.0) | 19 (23.5) | | |
| Serious AEs | 32 (14.5) | 13 (12.3) | 33 (13.5) | 11 (13.6) | | |
| Ocular | 22 (10.0) | 11 (10.4) | 15 (6.1) | 9 (11.1) | | |
| SE | 21 (9.5) | 11 (10.4) | 15 (6.1) | 9 (11.1) | | |
| Severe AEs | 29 (13.2) | 7 (6.6) | 13 (5.3) | 7 (8.6) | | |
| Ocular | 19 (8.6) | 5 (4.7) | 5 (2.0) | 6 (7.4) | | |
| SE | 18 (8.2) | 5 (4.7) | 5 (2.0) | 6 (7.4) | | |
| Disc. due to AEs | 2 (0.9) | 2 (1.9) | 2 (0.8) | 0 (0) | | |
| Death | 3 (1.4) | 0 (0) | 1 (0.4) | 0 (0) | | |

Source: Table 39, p128 of the re-submission

Benefits/harms

6.16 On the basis of direct evidence presented by the re-submission, there were no differences in the patient-relevant outcomes between ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy in the long-term. It remained unclear how effective ocriplasmin is with respect to the longer-term patient-relevant outcomes used as inputs to the model, including change in visual acuity ratings and preventing, rather than delaying, vitrectomy in the long-term. The ESC also noted the variable results across differences in quality of life as noted above.

Clinical claim

6.17 The re-submission described ocriplasmin as superior in terms of comparative effectiveness and inferior in terms of comparative safety over watchful waiting. This claim was adequately supported based on the primary outcome of the trials (non-surgical VMA resolution at day 28; the point where vitrectomy was not offered except if patients did not achieve VMA resolution, or at any point after day 1 if BCVA worsened by >2 lines (or 10 letters)), although it was inconsistent with the nominated comparator of watchful waiting ± vitrectomy. The PBAC previously accepted this claim, but considered it was not clear how effective ocriplasmin is with respect to the patient relevant-outcomes of improving visual function and of preventing, rather than delaying, vitrectomy in the long-term (Paragraph 7.8, Ocriplasmin November 2014 Public Summary Document).

6.18 For the purposes of the modelled economic evaluation, which was based solely on the results of the OASIS trial, the re-submission also explicitly claimed (p222 of the

submission) that ocriplasmin ± vitrectomy is superior to watchful waiting ± vitrectomy based on the clinical evidence presented. This claim was partially supported because, although a statistically significant difference was demonstrated for the primary outcome of the trial (see above); secondary outcomes in OASIS demonstrated:

- No significant difference across the arms in the proportion of patients treated with vitrectomy at Month 24. This is in contrast to the finding of a small but significant decrease in RR in patients treated with ocriplasmin at Month 6 based on all three trials.
- No significant difference across the arms in the proportion of patients with FTMH at baseline who achieved non-surgical FTMH closure at Month 24. This is in contrast to the finding of a significant difference in favour of ocriplasmin at Month 6 based on all three trials.
- No significant difference in the proportion of patients who achieved ≥ 2 or ≥ 3 lines improvement in BCVA at Month 24. This is in contrast to the finding of a small but significant improvement in patients treated with ocriplasmin at Month 6 based on all three trials.
- The mean difference in BCVA letters was not significantly different between treatment groups at Month 24. This is consistent with the findings at Day 28 and Month 6 based on all three trials.
- The proportion of people in the OASIS trial with more than a 5-point improvement on the VFQ-25 at 24 months was significantly greater (51.4% versus 30.1%).

- 6.19 The PBAC rejected (Paragraph 7.1, Ocriplasmin November 2014 Public Summary Document) the previous submission on the basis “that cost-effectiveness of ocriplasmin is highly uncertain because it remains unclear how effective ocriplasmin is with regard to the patient-relevant outcomes of improving visual function and of preventing rather than delaying vitrectomy in the long-term. Data from the OASIS trial, which provides follow-up to two years (compared with six months in the trials considered in the integrated co-dependent submission), indicated that there were no significant differences between visual acuity (as measured by visual activity indicators) or the proportion of patients who proceed to vitrectomy in those treated with ocriplasmin compared with control over a period of 24 months, however differences in the VFQ-25 over 2 years were observed.
- 6.20 The ESC noted that the PSCR stated that all of these outcomes showed trends favouring ocriplasmin, and the PSCR highlights the fact that the study was not powered to detect these outcomes.
- 6.21 Overall, the ESC was concerned that aspects of patient-relevant incremental effectiveness of ocriplasmin were not sustained over time, though this was modelled in the economic analysis. Rather, the most supported aspect of this modelled clinical claim was that ocriplasmin delayed rather than avoided vitrectomy in some patients.

Economic analysis

- 6.22 The re-submission presented a cost-utility analysis, based on individual patient data from OASIS to 24 months and then extrapolated to 31.5 years. The ESC noted that while differences in quality of life and non-surgically corrected VMA at 2 years were observed in the OASIS trial, there were no differences observed on other key outcomes, notably rates of vitrectomy at 2 years and visual acuity ratings. On the

basis of these findings, the ESC advised that a cost-utility analysis may be justified if the PBAC accepts these outcomes as possible indications of improved visual function, however the time horizon of the model also requires consideration since delay rather than prevention can also have economic benefit. The ESC, noting that even though VMT is a long-term disease, also considered that a short time horizon was more appropriate for the modelling the benefits of ocriplasmin due to doubts about sustained treatment effects. The ESC considered that a time horizon between 2 and 5 years would be more appropriate.

6.23 A summary of the model structure and rationale are presented in Table 9.

Table 9: Summary of model structure and rationale

| | |
|----------------------------------|--|
| Time horizon | 31.5 years in the model base case versus 2 years in trial (baseline age of cohort is 68.5 in decision tree and 69 in the Markov model; modelled to 100 years). |
| Outcomes | QALYs |
| Methods used to generate results | Cohort expected value analysis |
| Cycle length | Decision tree: to 6 months Markov model 6 month cycles |
| Transition probabilities | Decision tree: Markov model: Background mortality: Cycles 0 to 2, given survival: Cycles 3 to 61, given survival: |
| Discount rate | 5% for costs and outcomes |
| Software package | TreeAge |
| Half-cycle correction | Yes |

Source: compiled during the evaluation

6.24 The ESC welcomed the simpler structure to the modelled economic evaluation compared to that of the previous submission, but noted that substantial residual issues related to the assumptions behind pivotal inputs to the model. The key drivers of the model (see Table 10) included the time horizon where the trial evidence does not support extrapolation beyond 24 months, the greater proportion of the cohort in the ocriplasmin arm in the resolved health states beyond 6 months, the lower proportion in the ocriplasmin arm undergoing vitrectomy beyond 24 months, and the assumption that long-term utility in the “resolved with vitrectomy” health state is lower than the “resolved without vitrectomy” health state.

Table 10: Key drivers of the model

| Description | Method/Value | Impact |
|--|--|-------------------------------|
| Time horizon | 31.5 years; assumed from 24 month trial duration | High, favours ocriplasmin |
| Proportion in “resolved” health states beyond 6 months | In the model, 65.15% of the ocriplasmin arm commence in a resolved health state compared to 45.31% in the watchful waiting arm (difference: 19.84%). The <i>post hoc</i> outcome from TG-MV-006 and TG-MV-007 of “no anatomical abnormality regardless of vitrectomy” was not statistically significantly different at 6 months. | High, favours ocriplasmin |
| Proportion undergoing vitrectomy beyond 24 months | In the model, 30.52% of the ocriplasmin arm have undergone vitrectomy compared to 47.19% in the watchful waiting arm (difference: 16.67%) by 24 months. The secondary outcome “vitrectomy” in OASIS was not statistically significantly different at 24 months. | Moderate, favours ocriplasmin |
| Assumption that long-term utility is lower for “resolved with vitrectomy” compared to “resolved without vitrectomy”. | As the model assumes fewer patients in the watchful waiting arm undergo vitrectomy (-20.32% by the end of the model), there is a higher proportion of patients in the “resolved with vitrectomy” in the watchful waiting arm allocated a lower long-term utility. | Moderate, favours ocriplasmin |

Source: compiled during the evaluation

6.25 The results of the modelled economic evaluation are presented in Table 11.

Table 11: Results of the economic evaluation

| Component | OCRI | WW | Increment |
|---|---------------|---------------|---------------|
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2733 | 10.2060 | 0.0673 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |

Source: Table 104, p256 of the re-submission

- 6.26 This compared with ICERs of \$15,000/QALY - \$45,000/QALY in VMT only subgroup; \$45,000/QALY - \$75,000/QALY in VMT+ERM subgroup; \$15,000/QALY - \$45,000/QALY in VMT+MH subgroup; weighted= \$15,000/QALY - \$45,000/QALY from the integrated co-dependent submission.
- 6.27 The current model, based on OASIS, predicted a greater incremental proportion of patients would be resolved by 6 months (19.84%) compared to the previous model based on Trials TG-MV-006 and TG-MV-007 (12.33%). The starting distribution in the resolved and unresolved anatomical health states at 6 months was one of the key drivers of the current model given non-surgical and surgical resolution was permitted for the duration of the model; in the previous model, non-surgical resolution was not permitted beyond 6 months and surgical resolution was not permitted beyond 2.25 years. The proportion of patients without an anatomical defect (with or regardless of vitrectomy) was not reported in OASIS, but the information was provided in the PSCR.
- 6.28 The treatment effects in the model were both the time taken to transition to achieve VMT resolution and also whether the patient subsequently required a vitrectomy or not. The post hoc outcome from TG-MV-006 and TG-MV-007 of “no anatomical abnormality regardless of vitrectomy” was no different across arms at 6 months. However, OASIS found that there was a statistically significant difference for this

outcome at 24 months. The secondary outcome of vitrectomy in OASIS at 24 months indicated no difference across arms.

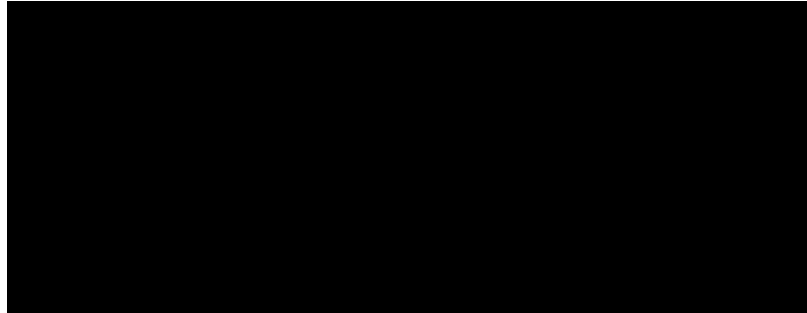
- 6.29 The PSCR presented two new sensitivity analyses of the modelled evaluation based on patient-level data in TG-MV-006 and TG-MV-007 using the ITT population and the subgroup with no ERM and an adhesion diameter $\leq 1500 \mu\text{m}$ (Table 12). The PSCR stated that it was not appropriate to pool OASIS, TG-MV-006 and TG-MV-007 due to unequal patient numbers across treatment groups, different comparators (sham injection vs intravitreal placebo) and designs of the respective trials.

Table 12: Results of the economic evaluation

| Component | OCRI | WW | Increment |
|---|---------------|---------------|---------------|
| Base case: OASIS (ITT) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2733 | 10.2060 | 0.0673 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Sensitivity 1: TG-MV-006 + TG-MV-007 (ITT) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2386 | 10.2009 | 0.0377 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Sensitivity 2: TG-MV-006 + TG-MV-007 (no ERM, adhesion $\leq 1500 \mu\text{m}$) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2631 | 10.2049 | 0.0582 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Sensitivity 3: TG-MV-006 + TG-MV-007 (VMT only) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2071 | 10.2450 | 0.0380 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Sensitivity 4: TG-MV-006 + TG-MV-007 (MH only) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 10.2170 | 10.1824 | 0.0346 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |

- 6.30 When transitions through the 6-month decision tree were informed by TG-MV-006 and TGMV-007 instead of OASIS, the ICER increased from \$15,000/QALY - \$45,000/QALY to \$75,000/QALY - \$105,000/QALY. The ESC considered that it was more informative to include all 3 trials in the economic analysis.
- 6.31 The re-submission stated that because all of the outcomes up to two years are trial-based, the stepped evaluation involved only extrapolation. It was argued that the extrapolated period reflected the longer-term consequences of events which accrued during the two-year trial. Figure 1 presents the ICER estimated by the current model by cycle. Noting that the ESC considered a 2-5 year range for the model time horizon more appropriate: at two years, the ICER was \$75,000/QALY - \$105,000/QALY and at five years, the ICER was \$45,000/QALY - \$75,000/QALY.

Figure 1: Estimated ICER by 6-monthly model cycle



Source: constructed during the evaluation

6.32 Sensitivity analyses using data from the two TG-MV trials showed that the ICER tripled. Furthermore other sensitivity analyses changing the utility values also had substantial impacts on the ICER.

Table 13: Results of sensitivity analyses conducted during the evaluation

| Univariate analyses | Incremental costs | Incremental effectiveness | Incremental cost-effectiveness |
|--|-------------------|---------------------------|--------------------------------|
| ITT (base case) | \$ [REDACTED] | 0.0673 | \$ [REDACTED] |
| Probability of VMT resolution at Day 28 set to estimates from TG-MV-006 and TG-MV-007 (pooled) | \$ [REDACTED] | 0.0454 | \$ [REDACTED] |
| Set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | 0.0395 | \$ [REDACTED] |
| Time horizon set to 2 years | \$ [REDACTED] | 0.0268 | \$ [REDACTED] |
| Time horizon set to 2 years + set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | 0.0235 | \$ [REDACTED] |
| Probability of VMT resolution at Day 28 set to estimates from TG-MV-006 and TG-MV-007 (pooled) + time horizon set to 2 years + set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | 0.0155 | \$ [REDACTED] |
| No MH at baseline (VMT only) subgroup | \$ [REDACTED] | 0.0861 | \$ [REDACTED] |
| Set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | 0.0619 | \$ [REDACTED] |
| MH at baseline subgroup | \$ [REDACTED] | 0.0263 | \$ [REDACTED] |
| Set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | -0.007 | Dominated# |
| VMT ± MH <250 µm subgroup | \$ [REDACTED] | 0.0726 | \$ [REDACTED] |
| Set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long-term QoL benefit via non-surgical resolution from 0.0127 to 0.0000) | \$ [REDACTED] | 0.0476 | \$ [REDACTED] |

Dominated because nearly all individuals in the watchful waiting arm received vitrectomy and resolved during the trial, which resulted in a higher proportion of individuals reaching the resolved health state in the modelled evaluation compared to the ocriplasmin arm (Markov traces on pages 253 and 254 of the re-submission).

Source: Table 106, pp259-261 of the re-submission; conducted during the evaluation

- 6.33 The results of the sensitivity analyses indicated that the model was most sensitive to the treatment effect at Day 28, and the assumption that long-term utility in the resolved health state is higher without vitrectomy compared to with vitrectomy and the time horizon. As discussed in Section C.3 of the commentary, the model assumed a long-term and on-going disutility associated with VMT resolution with vitrectomy which may represent double-counting, particularly as a disutility associated with the procedure itself (once-off) and adverse events are also applied in the model.
- 6.34 Given that the utilities were derived from a transformation algorithm which was based on VFQ-25 and EQ-5D responses in a different population of people with vision problems (wet age related macular degeneration (AMD)), and the relationship between the two instruments was not particularly strong (as stated in the published transformational algorithm), these values may not reflect the true differences in the utility levels between the different health states. The ESC considered these values may not reflect the true differences in the utility levels between the different health states of patients with VMT.

- 6.35 However, the ESC noted that there were different utilities applied in the health states for ‘resolved with vitrectomy’ and ‘resolved without vitrectomy’ (for example, 24 months, 0.889 and 0.9094, respectively). The ESC considered that there was no reason for this difference and noted that the sensitivity analysis (“Set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long term QoL benefit via non-surgical resolution from 0.0127 to 0.0000)”) increased the ICER from the base case of \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$75,000/QALY.
- 6.36 The ESC noted that the scenario analysis of “Probability of VMT resolution at Day 28 set to estimates from TG-MV-006 and TG-MV-007 (pooled) + time horizon set to 2 years + set utility for resolved with vitrectomy equal to utility resolved without vitrectomy (ie, long term QoL benefit via non-surgical resolution from 0.0127 to 0.0000)” increased the ICER from the base case of \$15,000/QALY - \$45,000/QALY to \$105,000/QALY - \$105,000/QALY.
- 6.37 The ESC noted that the model allowed patients to have a vitrectomy after the 2-year period (informed by the trial data between 12 and 24 months). Under the assumption that vitrectomy is not permitted beyond 2 years, the ICER increased slightly from the base case of \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY.
- 6.38 The ESC noted the proposal in the PSCR (p2) to exclude patients with FTMH from the eligible patient population. Although the result of the post hoc subgroup of “No ERM, adhesion $\leq 1500 \mu\text{m}$ and No MH” was not presented, the ICER for the VMT only (ie No MH) subgroup was \$15,000/QALY - \$45,000/QALY when based on OASIS and \$75,000/QALY - \$105,000/QALY when based on TG-MV-006+TG-MV-007.
- 6.39 Overall, the ESC considered that the revised model was appropriately re-structured from the original submission with appropriate health states, but that the inputs used in the analysis relied on over-optimistic assumptions that favoured ocriplasmin.
- 6.40 The PBAC agreed with the ESC about the improved structure, but considered that, by applying more reasonable but less optimistic assumptions in the model as outlined below, the cost-effectiveness was high and uncertain.
- 6.41 The PBAC also agreed with the ESC that including all trials in the economic analysis would have been more appropriate. The PBAC did not accept the arguments raised by sponsor and noted the potential for leakage to ERM and greater FTMH size populations. The PBAC noted that comparator response rates for the primary outcome were similar across the 3 trials (particularly across OASIS and TG-MV-007). When informed by TG-MV-006 and TGMV-007 instead of OASIS, the ICER increased from \$15,000/QALY - \$45,000/QALY to \$75,000/QALY - \$105,000/QALY. The PBAC expected that the ICER when including all trials in the analysis would lie between these two values.
- 6.42 The PBAC considered that the 31-year time horizon was not appropriate, because even though VMT is a long-term condition, the long-term incremental effectiveness of ocriplasmin is, at best, weakly substantiated. The PBAC noted that the pre-PBAC response argued that a time horizon of at least ten years is necessary and that the ICER increased \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY, when the time horizon set to 10 years rather than 31.5 years. The PBAC agreed with

ESC advised that a short-time horizon (2-5 years) would be more appropriate for the modelling the benefits of ocriplasmin.

- 6.43 The PBAC also agreed with ESC that there was no reason for different utilities to be applied in the health states for 'resolved with vitrectomy' and 'resolved without vitrectomy'. The PBAC noted that the pre-PBAC response removed the disutility associated with vitrectomy-induced resolution (0.0127) in a sensitivity analysis.
- 6.44 The PBAC maintained its view that the longer-term value of ocriplasmin was not clear. The PBAC considered that a shorter 5-year time horizon would help address its other concerns of applying over-optimistic inputs (such as non-statistically significant differences in rates of vitrectomy at 2 years and the applying QoL/utility transformation differences across the different health states that may not be appropriate) in a life time model.
- 6.45 The PBAC therefore considered that, for the cost-effectiveness of ocriplasmin to be acceptable, a price reduction would be required consistent with addressing the following parameters applied to the model as presented in the re-submission:
- time horizon to be set to 5 years
 - utility for "resolved with vitrectomy" to be set equal to "utility resolved without vitrectomy" (ie, long term QoL benefit via non-surgical resolution reduced from 0.0127 to 0.0000)"
 - resulting ICER to be no greater than the re-submission's base case of \$15,000/QALY - \$45,000/QALY.

Drug cost/eye

- 6.46 \$[REDACTED]. Ocriplasmin is a single intravitreal injection, proposed for use once per lifetime per eye. As VMT is predominantly a unilateral condition, the drug cost/eye approximates the drug cost/patient.

Estimated PBS usage & financial implications

- 6.47 This re-submission was not considered by DUSC.
- 6.48 Consistent with the original integrated co-dependent submission, an epidemiological approach was taken in the current submission to estimate the cost to the government of ocriplasmin for the requested listing of VMT. Although the approach was mostly unchanged, new eligibility criteria and revised parameters (based on comments by DUSC) were incorporated.

Table 14: Estimated use and financial implications

| | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|------|------|------|------|------|
| Estimation of use and costs of ocriplasmin | | | | | |
| Total eligible population | █ | █ | █ | █ | █ |
| Total treated population | █ | █ | █ | █ | █ |
| Cost to the PBS/RPBS for ocriplasmin (less co-payment) | \$█ | \$█ | \$█ | \$█ | \$█ |
| Estimated financial implications for the PBS/RPBS or the NIP | | | | | |
| Cost to the PBS/RPBS for ocriplasmin (less co-payment) | \$█ | \$█ | \$█ | \$█ | \$█ |
| Estimated financial implications for government health budgets | | | | | |
| Number of OCTs required | █ | █ | █ | █ | █ |
| Cost to MBS for OCTs (85% benefit) | \$█ | \$█ | \$█ | \$█ | \$█ |
| Number of ocriplasmin administrations | █ | █ | █ | █ | █ |
| Cost to MBS for administration of ocriplasmin (85% benefit) | \$█ | \$█ | \$█ | \$█ | \$█ |
| Vitrectomies avoided | █ | █ | █ | █ | █ |
| Net cost to government for vitrectomies (surgery only) | -\$█ | -\$█ | -\$█ | -\$█ | -\$█ |
| Vitrectomy related cataracts avoided | █ | █ | █ | █ | █ |
| Net cost to government for vitrectomy related cataracts | -\$█ | -\$█ | -\$█ | -\$█ | -\$█ |
| Net cost of ocriplasmin to the health budget | \$█ | \$█ | \$█ | \$█ | \$█ |

Italics show differences due the correction of the proportion of macular holes associated with VMT from 73% used in the excel file to 74% stated in the re-submission and reported in the source publication.

Source: Tables 109, 110, 111, 113, 114, 115, 117, 118, 121 and 122, pp261-279 of the re-submission; 'Ocriplasmin Section E November 2015 PBAC submission.xls

The redacted table above shows that at year 5, the estimated number of patients will be less than 10,000 and the estimated cost to PBS will be less than \$10 million.

- 6.49 The financial implications presented in the integrated co-dependent submission estimated a net cost of ocriplasmin to the health budget of less than \$10 million in Year 1 increasing to less than \$10 million in Year 5.
- 6.50 Although the estimated incidence of VMT appeared to be generally reasonable, there was a potential for the number of eligible patients to be greater than the estimate in the re-submission, notwithstanding the potential to misdiagnose ERM or the true adhesion diameter, given:
- The proportion of patients who meet the newly proposed eligibility criteria (█%) may be underestimated given █% in OASIS met this criteria; and
 - The prevalent population of unresolved VMT may be higher than the incident population of VMT since this estimate was based on the assumption from the integrated co-dependent submission that patients are only considered for active treatment within the first two years of diagnosis. The ESC considered that this assumption was unreasonable and it was not used to derive the current estimates.
- 6.51 There was potential for the net cost/year for the PBS to be greater than that estimated in the re-submission (a) given that the eligible population and number of patients treated may have been underestimated; (b) due to the potential use of ocriplasmin outside the requested listing (as the financial estimates were most sensitive to accounting for use in patients with ERM and/or adhesion diameter

>1500 µm (patients excluded by the restriction)): and (c) the uptake assumptions. The ESC considered there was a risk that ocriplasmin may be used outside of the restriction proposed in the submission.

Financial Management – Risk Sharing Arrangements

- 6.52 The PBAC considered that the cost to Government may be underestimated, at the proposed price, due to leakage outside the proposed restriction, for example, into the patient population with ERM or with adhesion diameter >1500 µm, which together may represent 57% of the total VMT population. For this reason, the PBAC recommended that a Risk Share Arrangement be negotiated, suggesting that a rebate should apply where the majority of Commonwealth expenditure is reimbursed above any financial cap, which reflects utilisation above the relevant patient estimate in the sponsor's submission.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority required (TELEPHONE) listing of ocriplasmin for the treatment of vitreomacular traction (VMT) excluding patients with epiretinal membrane (ERM) or vitreomacular adhesion diameter >1500 µm, on the basis of appropriately adjusted estimates of cost-effectiveness compared to watchful waiting with or without vitrectomy.
- 7.2 The PBAC noted that, compared to the November 2014 submission, the requested restriction excluded patients with (i) an adhesion diameter >1500 µm and/or (ii) an epiretinal membrane and added criteria to align the requested restriction with the inclusion/exclusion criteria of the trial evidence. The PBAC recalled that the necessity for strict cold chain supply and storage (ensuring the product remains at all times at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ requires specialised refrigeration equipment), together with the importation on a patient by patient basis directly from the manufacturing site (within 7-24 days) and the requirements for preparation and administration into the eye, would mean that the usual dispensing arrangements through community pharmacists may not be able to be implemented simply. Although the re-submission stated that pharmacy involvement in the PBS dispensing of ocriplasmin has been identified and a process has been confirmed, no details of this pharmacy involvement were provided in the re-submission. The PBAC requested the Department explore the most appropriate mechanism to list ocriplasmin on the PBS consistent with the processes developed for its supply up to the point of administration into the eye. Further, the PBAC noted that the submission's DPMQ included fees and mark-ups associated with a community pharmacy listing and considered that any financial implications for the listing over these fees and mark-ups should be borne by the Sponsor.
- 7.3 The PBAC recalled that ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy was previously considered to be the appropriate comparator.
- 7.4 The PBAC noted that the sham-controlled OASIS randomised trial was presented in addition to the two randomised trials (TMG-MV-006 and TG-MV-007) comparing

ocriplasmin with placebo (watchful waiting), which were presented in the November 2014 submission. Despite the potential for placebo results to differ from sham results, the PBAC noted that the results across the trials did not indicate that this was a cause for concern in interpreting the results across the three trials.

- 7.5 The PBAC recalled its view in November 2015, that the primary outcome of the ocriplasmin trials, “non-surgical VMA resolution at Day 28”, may be a reasonable surrogate outcome, but any relationship between non-surgical VMA resolution and extent of changes in visual acuity or visual disturbance or need for vitrectomy, which would be considered as patient-relevant outcomes, was not presented in the submission. The PBAC also noted that any relationship between another potential surrogate outcome, FTMH closure, and extent of changes in visual acuity or visual disturbance or need for vitrectomy, was not explored in the submission. The PBAC considered the evidence provided in the re-submission did not modify the Committee’s previous view, noting that data was now available for up to 24 months of follow-up.
- 7.6 The re-submission claimed that ocriplasmin is superior in effectiveness and inferior in safety compared with watchful waiting, as claimed in the November 2014 submission. The PBAC accepted these claims for effectiveness, but noted that the claim for effectiveness was most convincingly demonstrated for the outcome of “non-surgical VMT resolution 28 days following treatment”. However, the PBAC considered that the hearing had highlighted some of the negative impacts to patients following a surgical intervention. Therefore the PBAC considered that the clinical value of ocriplasmin with respect to the patient-relevant outcomes of improving visual function and of preventing, rather than delaying, vitrectomy in the long-term remained not clear, but acknowledged that ocriplasmin provides a net clinical benefit to some patients.
- 7.7 The PBAC recalled its concerns with the economic model presented in the November 2014 which, as constructed, did not form a suitable basis for PBAC consideration. The PBAC agreed with the ESC that the revised model was appropriately re-structured from the original submission with more appropriate health states.
- 7.8 The PBAC noted that the estimated PBS usage and financial implications were updated from the November 2014 submission incorporating new eligibility criteria and revised parameters (based on the previous DUSC consideration). The PBAC considered that the cost to Government may be underestimated, at the proposed price, due to leakage outside the proposed restriction, for example, into the patient population with ERM or with adhesion diameter >1500 µm, which together may represent 57% of the total VMT population. For this reason, the PBAC recommended that a Risk Share Arrangement be negotiated, suggesting that a rebate should apply where the majority of Commonwealth expenditure is reimbursed above any financial cap, which reflects utilisation beyond the Sponsor’s estimates.
- 7.9 The PBAC recalled that MSAC had deferred the application for optical coherence tomography (OCT) until such time as the PBAC makes a positive recommendation regarding the corresponding PBS listing of ocriplasmin. In making its recommendation, the PBAC noted that no particular issue was identified that might be relevant to MSAC deliberations. The PBAC noted that the restriction is dependent on the outcome of the MSAC deliberations regarding OCT.

- 7.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that ocriplasmin should not be treated as interchangeable on an individual patient basis with any other medicine in the PBS.
- 7.11 The PBAC advised that ocriplasmin is not suitable for prescribing by nurse practitioners, as it must be prescribed by an ophthalmologist.
- 7.12 The PBAC recommended that the Early Supply rule should not apply, as patients are only treated once with ocriplasmin.
- 7.13 The re-submission is not eligible for an Independent Review, because the PBAC made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item:

Restriction to be finalised

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer | |
|---|-------------|----------------|-----------------------------------|-------|
| OCRIPLASMIN 0.5 mg/ 0.2 mL injection, 1x 0.2 mL vial | 1 | 0 | Jetrea | Alcon |

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.