5.6 OCRIPLASMIN 0.5 mg / 0.2 mL injection, 1 x 0.2 mL vial, Jetrea®, Alcon Laboratories (Australia) Pty Ltd.

1 Purpose of Application

1.1 To request an Authority Required listing of ocriplasmin for the treatment of vitreomacular traction (VMT) including those with full-thickness macular hole (FTMH).

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OCRIPLASMIN Vial, 0.5 mg/0.2 mL	1	0	Jetrea®	Alcon

Authority required
Vitreomacular traction (VMT) including those with full-thickness macular hole (FTMH).

Criteria:
Must be treated by an ophthalmologist.
The condition must be confirmed by optical coherence tomography (OCT).
The condition must not be a FTMH of diameter >400µm (as determined by OCT).
Patient must not have received prior treatment with ocriplasmin in the same eye.

2.1 The basis for the requested listing was a cost utility analysis comparing ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy with OCT at both arms.

2.2 The PBAC noted the requested restriction does not exclude patients with age-related macular degeneration, who were excluded in the clinical trials presented in the submission.

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

3 Background

3.1 Ocriplasmin was TGA registered on 9 Oct 2014 for the following indication: "JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns."

3.2 This application has not been considered by PBAC previously.

3.3 Elements of this application were integrated with an application to MSAC requesting listing of optical coherence tomography (OCT) for use in the context of ocriplasmin.

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 epiretinal membrane (ERM).

4.2 There is currently one treatment available for these patients (vitrectomy). The requested listing was intended to provide another alternative which achieves similar outcomes when treatment with ocriplasmin is successful. When unsuccessful, patients would require treatment with both ocriplasmin and vitrectomy.

4.3 The PBAC noted that the necessity for strict cold chain supply and storage (ensuring the product remains at all times at -20°C ± 5°C requires specialised refrigeration equipment), together with the requirements for preparation and administration into the eye, means that the usual dispensing arrangements through community pharmacists may not be appropriate. Further details were needed on the proposed arrangements. For example if ocriplasmin is to be stored overseas and imported into Australia when it has been prescribed for a patient, this could result in delays to treatment (the PSCR advised that this should be within 7-24 days to avoid a repeat OCT), especially for rural or remote patients. These issues may also affect both the appropriate type of PBS listing (e.g. Section 100 arrangements) and the overall costs of supplying ocriplasmin, beyond its acquisition cost.

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

5 Comparator

5.1 The submission stated that the nomination of the comparator depends on the severity of the symptoms and macular abnormality of the individual. The submission nominated the following comparators:

VMT, no MH	VMT + MH
Watchful-waiting which can ultimately lead to vitrectomy in a proportion of patients whose condition progresses to a FTMH or where symptoms are intolerable	Vitrectomy

The comparison would be best described as that of:

ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy.

5.2 The PBAC considered the nominated comparators are appropriate.

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.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item. However the PBAC noted consumer inputs via the MSAC process 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. Thus there is a preference for better and less invasive investigations and treatments.

Clinical trials

6.3 The submission was based on two direct randomised trials (TG-MV-006 and TG-MV-007) comparing ocriplasmin with placebo.

6.4 Details of the trials presented in the submission are provided in the table below.

Studies and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
TG-MV-006 (NCT00781859)	Clinical Study Report. Ocriplasmin. 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 ocriplasmin for vitreomacular traction and macular holes.	*New England Journal of Medicine* 2012, 367(7):606-15
TG-MV-007 (NCT00798317)	Clinical Study Report. Ocriplasmin. 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 ocriplasmin for vitreomacular traction and macular holes.	*New England Journal of Medicine* 2012, 367(7):606-15
TG-MV-012 (NCT01287988)	Follow-up Study to Assess Visual Function in Subset of Patients Who Have Previously Participated in the TG-MV-006 and TG-MV-007 Ocriplasmin Studies.	clinicaltrials.gov
TG-MV-014 (NCT01429441)	Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS)	clinicaltrials.gov
TG-MV-001 (NCT00123279)	Intravitreal Microplasmin in Patients Undergoing Surgical Vitrectomy	clinicaltrials.gov
	de Smet, M. D., Gandorfer, A., Stalmans, P., Veckeneer, M., Feron, E., Pakola, S., & Kampik, A. Microplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy: the MIVI I trial.	Ophthalmology 2009, 116(7), 1349-55.
TG-MV-002 (NCT00412451)	A Multicenter Study to Compare Multiple Doses of Intravitreal Microplasmin Versus Sham Injection for Treatment of Patients With Diabetic Macular Edema (DME) (MINI-II)	clinicaltrials.gov
TG-MV-003 (NCT00412958)	A Study of the Safety and Efficacy of Microplasmin to Induce a Posterior Vitreous Detachment (MIVI III)	clinicaltrials.gov
	Benz, M. S., Packo, K. H., Gonzalez, V., Pakola, S., Bezner, D., Haller, J. A., & Schwartz, S. D. A placebo-controlled trial of microplasmin intravitreous injection to facilitate posterior vitreous detachment before vitrectomy.	Ophthalmology 2010, 117(4), 791-7.
TG-MV-004 (NCT00435539)	A Study to Compare Multiple Doses Intravitreal Microplasmin for Treatment of Patients With Vitreomacular Traction (MIVI-IIt).	clinicaltrials.gov

	Stalmans, P., Delaey, C., de Smet, M. D., van Dijkman, E., & Pakola, S. (2010). Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial).	Retina, 30(7), 1122-7.
TG-MV-005 (NCT00913744)	Safety and Efficacy Study of Intravitreal Ocriplasmin in Subjects With AMD With Focal Vitreomacular Adhesion (MIVI-5).	clinicaltrials.gov
TG-MV-008 (NCT01055535)	Safety and Efficacy Study of Microplasmin in for Non-Surgical Treatment of Focal Vitreomacular Adhesion (MIVI-8).	clinicaltrials.gov
TG-MV-009 (NCT00986362)	Clinical Trial of Intravitreal Microplasmin in Infants and Children Scheduled for Vitrectomy (MIC).	clinicaltrials.gov
TG-MV-010 (NCT01159665)	The Purpose of This Study is to Evaluate the Pharmacokinetic Properties of Intravitreal Ocriplasmin Prior to Planned Primary Pars Plana Vitrectomy (PPV) (MIVI-10).	clinicaltrials.gov
JSEI-TG-AMD-001 (NCT00996684)	Study of Intravitreal Microplasmin in Relieving Vitreo-Macular Adhesion in Neovascular Age-related Macular Degeneration (AMD).	clinicaltrials.gov

6.5 The key features of the direct randomised trials are presented in the table below.

Trial	N	Design / duration	Risk of bias	Patient population	Outcomes	Used in model
TG-MV-006	326	R, BD, PC, MC, 6mths	*Low*	≥18years; VMT±MH; OCT confirmed	VMA resolution; FTMH closure; vitrectomy	IPD in FAS
TG-MV-007	326					
Pooled	FAS (TG-MV-006+TG-MV-007); N = 648 (4 excluded);					FAS used

DB=double blind; FAS=full analysis set; IPD=individual patient data; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; PC=placebo-controlled
Source: compiled during the evaluation

6.6 The risk of bias in the ocriplasmin trials was low. Patients enrolled in the trials were considered to be broadly representative of those for whom listing is sought. All patients in the trials, whether randomised to ocriplasmin ± vitrectomy or placebo ± vitrectomy, had a diagnosis of VMT ± MH using OCT as one of many diagnostic tests.

Comparative effectiveness

6.7 The table below summarises the primary outcome of the ocriplasmin trials: non-surgical vitreomacular adhesion (VMA) resolution at Day 28. Whilst this is a surrogate outcome, the submission did not explore the relationship of VMA resolution and changes in visual acuity or visual disturbance (key outcomes in the modelled economic evaluation), which would be considered patient-relevant outcomes. An assessment of the relationship of VMA resolution (and FTMH closure) and changes in visual acuity and visual disturbance was conducted during the evaluation according to the framework for evaluating proposed surrogate measures and their use in the submissions to the PBAC published by the Surrogate to Final Outcome Working group of the PBAC (STFOWG). This assessment indicated that VMA resolution from vitrectomy resulted in an improvement or maintenance of visual acuity, which may be applicable to ocriplasmin. No data were presented exploring the relationship of VMA resolution and improvement in visual disturbance. The ESCs noted that there were limited data on the natural spontaneous resolution of VMA or VMT with MH, and the basis for the resolution rates in the model were not clearly justified in the economic evaluation.

Results of the primary outcome: non-surgical VMA resolution (Day 28) across the direct randomised trials (FAS)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
TG-MV-006	61/219 (27.9)	14/107 (13.1)	**0.15 (0.06, 0.23)**	**7 (4, 17)**	**2.13 (1.25, 3.63)**
TG-MV-007	62/245 (25.3)	5/81 (6.2)	**0.19 (0.12, 0.27)**	**5 (4, 8)**	**4.10 (1.71, 9.84)**
Pooled	123/464 (26.5)	19/188 (10.1)	**0.17 (0.12, 0.23)**	**6 (4, 8)**	**2.69 (1.44, 5.05)**

Source: Table 28, p96 of the submission
NNT were calculated during the evaluation by (1/RD).

6.8 An outcome used in the modelled economic evaluation was FTMH closure in the prespecified subgroup of patients with VMT + MH. The results for FTMH closure reported in the ocriplasmin trials are presented in the table below. The assessment of FTMH closure as a surrogate measure for visual acuity indicated that visual acuity and visual disturbance were improved in those with FTMH closure.

Results of the secondary outcome: non-surgical FTMH closure (Day 28, Month 6) across the direct randomised trials (FAS)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
Day 28					
TG-MV-006	25/57 (43.9)	4/32 (12.5)	**0.31 (0.14, 0.49)**	**3 (2, 7)**	**3.51 (1.34, 9.19)**
TG-MV-007	18/49 (36.7)	1/15 (6.7)	**0.30 (0.12, 0.49)**	**3 (2, 8)**	**5.51 (0.80, 37.92)**
Pooled	43/106 (40.6)	5/47 (10.6)	**0.31 (0.18, 0.43)**	**3 (3, 6)**	**3.84 (1.62, 9.08)**
Month 6					
TG-MV-006	26/57 (45.6)	5/32 (15.6)	**0.30 (0.12, 0.48)**	**3 (2, 8)**	**2.92 (1.24, 6.85)**
TG-MV-007	17/49 (34.7)	3/15 (20.0)	0.15 (-0.10, 0.39)	NA	1.73 (0.59, 5.12)
Pooled	43/106 (40.6)	8/47 (17.0)	**0.25 (0.10, 0.39)**	**4 (3, 10)**	**2.39 (1.22, 4.67)**

Source: Tables 29 to 33, pp101-116 of the submission
NNT were calculated during the evaluation by (1/RD).

6.9 A patient-relevant outcome, change in best corrected visual acuity, is presented in the table below. No differences between the treatment arms were observed at 28 days or at 6 months.

Mean change from baseline in BCVA letters (FAS)

Trial	Ocriplasmin n/N (%): mean (SD)		Placebo n/N (%): mean (SD)		Mean difference (95%CI)
28 days					
TG-MV-006	[redacted]				
TG-MV-007	[redacted]				
Pooled	464/464 (100%)	2.60	187/188 (99.47%)	2.72	-0.12 (-1.32, 1.09)
6 months					
TG-MV-006	[redacted]				
TG-MV-007	[redacted]				
Pooled	464/464 (100%)	3.55	187/188 (99.47%)	2.45	1.11 (-0.64, 2.85)

Source: Table 34, p120 of the submission

6.10 However the submission claimed an improvement in BCVA following ocriplasmin based on dichotomising selected secondary results (with respect to six thresholds of changes in letters of BCVA from baseline at Month 6) from the direct randomised trials. The results summarised below are the analysis of patients who had 2 or more

lines improvement in BCVA. Even if these results are true differences, the ESCs queried whether the extent of BCVA improvement exceeded the minimal clinically important differences accepted by PBAC in the context of other ocular diseases. For example the PBAC has previously considered that a 10-letter gain represents a clinically significant improvement in vision related quality of life (ranibizumab DME PSD, November 2013), where ≥10 letters gain/loss is equal to ≥2 lines gain/loss. The ESCs also noted that the extent of BCVA improvement is influenced by how severe the BCVA loss is prior to treatment.

Results at Month 6 for patients with ≥2 lines improvement in best corrected visual acuity (BCVA) (FAS)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
TG-MV-006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TG-MV-007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	130/464 (28.0)	32/188 (17.0)	**0.11 (0.04, 0.18)**	**9 (5, 25)**	**1.66 (1.17, 2.35)**

Source: Table 33, p115 of the submission
NNT were calculated during the evaluation by (1/RD).

6.11 The results of vitrectomy required at Day 28 and at 6 months from the ITT analyses are shown in the table below, as this was considered to be another patient-relevant outcome.

Results of vitrectomy required at Day 28 and Month 6 (FAS)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	*NNT (95% CI)*	RR (95% CI)
Day 28					
TG-MV-006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TG-MV-007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	3/464 (0.6)	2/188 (1.1)	-0.00 (-0.02, 0.02)	*NA*	0.52 (0.04, 6.22)
Month 6					
TG-MV-006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TG-MV-007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	82/464 (17.7)	50/188 (26.6)	**-0.08 (-0.16, -0.01)**	***13 (6, 100)***	**0.68 (0.50, 0.93)**

Source: Tables 31, pp107 of the submission
NNT were calculated during the evaluation by (1/RD).

6.12 Although the ITT analysis showed that there were fewer vitrectomies at 6 months in the ocriplasmin arm than in the placebo arm, the ESCs noted that successful non-surgical VMA resolution at Day 28 did not appear to reliably predict avoidance of vitrectomy by the end of the trial. About 20% and 13% of patients receiving ocriplasmin in TG-MV-006 and TG-MV-007, respectively, subsequently required a vitrectomy.

Proportion of Subjects who Received Vitrectomy in the Study Eye as of Day 28 and End of Study by Outcome of the Primary and Key Secondary Efficacy Endpoints (Full Analysis Set)
[TABLE REDACTED]

6.13 The submission relied heavily on the results of subgroup analyses. Patients with a macular hole were identified as a prespecified subgroup in the trials, with the implied claim that the presence of a macular hole predicts treatment effect variation following ocriplasmin in patients with VMT. This may be biologically plausible if the presence

of a macular hole is associated with greater distortion of vision, or suggests that the patient's VMT will progress differently (e.g. less likely to resolve without an intervention than a patient VMT without a macular hole). However, there was little information provided on the natural history of untreated VMT to judge whether there are different prognoses across VMT subtypes. In addition, the ESCs also noted that the Food and Drug Administration in the United States has concluded with reference to the same two trials, that ocriplasmin is not recommended for the treatment of FTMH associated with VMA because closure of FTMH was a secondary outcome. After correct adjustment for multiplicity, the analysis for study TG-MV-006 showed statistical significance (P<0.005) while the analysis for study TG-MV-007 did not (p=0.354) (p19, Centre for Drug Evaluation and Research, Application number 125422Orig1s000, Medical Review(s)).

6.14 The modelled economic evaluation further categorised patients with VMT without a macular hole into those with epiretinal membrane (VMT + ERM) and without epiretinal membrane (VMT only). No justification for this further categorisation was provided in the submission. The implied claim was that the presence of ERM predicts treatment effect variation following ocriplasmin in patients with VMT without a macular hole. The ESCs noted that the results of individual patient data (IPD)-based subgroup analyses were provided with the PSCR in response to a request in the commentary to support the reliance of the modelled economic evaluation on subgroup analyses. These analyses were not independently evaluated.

6.15 The results shown in the tables below for prespecified subgroups indicated that the presence of a macular hole (irrespective of ERM) does not reliably predict any treatment effect variation for VMA resolution at Day 28 or vitrectomy at 6 months.

Results of non-surgical VMA resolution (Day 28) across the direct randomised trials (FTMH subgroups)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
FTMH present subgroup (±ERM)					
TG-MV-006	27/57 (47.4)	9/32 (28.1)	0.19 (-0.01,0.40)	NA	1.68 (0.91, 3.12)
TG-MV-007	26/49 (53.1)	3/15 (20.0)	**0.33 (0.08, 0.58)**	**3 (2, 13)**	2.65 (0.93, 7.55)
Pooled	53/106 (50.0)	12/47 (25.5)	**0.25 (0.09, 0.40)**	**4 (3, 11)**	**1.89 (1.11, 3.22)**
FTMH absent subgroup (±ERM)					
TG-MV-006	34/162 (21.0)	5/75 (6.7)	**0.14 (0.06, 0.23)**	**7 (4, 17)**	**3.15 (1.28, 7.73)**
TG-MV-007	36/196 (18.4)	2/66 (3.0)	**0.15 (0.09, 0.22)**	**7 (5, 11)**	**6.06 (1.50, 24.49)**
Pooled	70/358 (19.6)	7/141 (5.0)	**0.15 (0.10, 0.20)**	**7 (5, 10)**	**3.81 (1.79, 8.12)**
		Test for interaction	p=0.23	NA	p=0.14

Source: Table 31, p85 in CSR TG-MV-006; Table 31, p86 in CSR TG-MV-007
NNT was calculated by (1/RD) and test for interaction were conducted during the evaluation.

Proportion who received vitrectomy in the study eye by 6 months across the direct randomised trials (FTMH subgroups)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)
FTMH present subgroup (±ERM)				
TG-MV-006	26/57 (45.6)	19/32 (59.4)	-0.14 (-0.35, 0.08)	0.77 (0.51, 1.15)
TG-MV-007	21/49 (42.9)	8/15 (53.3)	-0.10 (-0.39, 0.18)	0.80 (0.45, 1.43)
Pooled	47/106 (44.3)	27/47 (57.4)	-0.13 (-0.30, 0.05)	0.78 (0.56, 1.08)
FTMH absent subgroup (±ERM)				
TG-MV-006	[redacted]	[redacted]	[redacted]	[redacted]

TG-MV-007	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	35/358 (9.8)	23/141 (16.3)	-0.06 (-0.13, 0.01)	**0.61 (0.37, 0.99)**

Source: Table 37, p91 CSR TG-MV-006; Table 37, p92 CSR TG-MV-007

6.16 Although not statistically significant, the limited data available for BCVA where baseline BCVA was also reported across the prespecified subgroups (TG-MV-006 only) suggested patients with a macular hole had worse baseline BCVA and a possible trend to increased BCVA effect.

Change from baseline in BCVA in the study eye by Day 28 and 6 months for TG-MV-006 (FTMH subgroups)

Follow-up	Number in subgroup		Mean baseline BCVA (SD)		Mean change from baseline BCVA (SD)		p-value for change between groups
	Ocriplasmin	Placebo	Ocriplasmin	Placebo	Ocriplasmin	Placebo	
FTMH present subgroup (±ERM)							
Day 28	[redacted]						
6 months							
FTMH absent subgroup (±ERM)							
Day 28	[redacted]						
6 months							

Source: Table 41, p98 CSR TG-MV-006

6.17 The results shown in the tables below for prespecified subgroup analyses indicated that presence of ERM (irrespective of macular hole) does not reliably predict treatment effect variation for the primary outcome of VMA resolution at Day 28 when assessed using relative risk, but may predict treatment effect variation when assessed using risk difference. There were generally no differences between the arms for these subgroups with respect to vitrectomy at 6 months although there were numerically fewer in the ocriplasmin arms. The ESCs noted that NICE had excluded the subgroup with ERM in its recommendations.

Results of non-surgical VMA resolution (Day 28) across the direct randomised trials (ERM subgroups)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
ERM present subgroup (±MH)					
TG-MV-006	6/86 (7.0)	0/35 (0.0)	**0.07 (0.00,0.14)**	**14 (7, 1,000)**	5.38 (0.31,93.01)
TG-MV-007	10/98 (10.2)	1/33 (3.0)	0.07 (-0.01,0.16)	NA	3.37 (0.45,25.32)
Pooled	16/184 (8.7)	1/68 (1.5)	**0.07 (0.02,0.12)**	**14 (8, 50)**	3.94 (0.76, 20.43)
ERM absent subgroup (±MH)					
TG-MV-006	52/128 (40.6)	14/72 (19.4)	**0.21 (0.09,0.34)**	**5 (3, 11)**	**2.09 (1.25, 3.50)**
TG-MV-007	49/142 (34.5)	3/47 (6.4)	**0.28 (0.18,0.39)**	**4 (3, 6)**	**5.41 (1.77, 16.54)**
Pooled	101/270 (37.4)	17/119 (14.3)	**0.25 (0.17,0.33)**	**4 (3, 6)**	**2.97 (1.16, 7.61)**
		Test for interaction	**p=0.0002**	NA	p=0.74

Source: Table 31, p85 in CSR TG-MV-006; Table 31, p86 in CSR TG-MV-007
NNT and were calculated by (1/RD) and test for interaction were conducted during the evaluation.

Proportion who received vitrectomy in the study eye by 6 months across the direct randomised trials (ERM subgroups)

Trial	Ocriplasmin n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)
ERM present subgroup (±MH)				
TG-MV-006	16/86 (18.6)	7/35 (20.0)	-0.01 (-0.07, 0.14)	0.93 (0.42, 2.06)
TG-MV-007	11/98 (11.2)	8/33 (24.2)	-0.13 (-0.29, 0.03)	0.46 (0.20, 1.05)
Pooled	27/184 (14.7)	15/68 (22.1)	-0.07 (-0.18, 0.04)	0.66 (0.33, 1.31)
ERM absent subgroup (±MH)				
TG-MV-006	27/128 (21.1)	24/72 (33.3)	-0.12 (-0.25, 0.01)	0.63 (0.40, 1.01)
TG-MV-007	24/132 (16.9)	11/47 (23.4)	-0.05 (-0.19, 0.09)	0.78 (0.41, 1.46)
Pooled	51/260 (19.6)	35/119 (29.4)	-0.09 (-0.18, 0.01)	**0.68 (0.47, 0.99)**

Source: Table 37, p91 CSR TG-MV-006; Table 37, p92 CSR TG-MV-007

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

Comparative harms

6.18 The adverse events reported in the ocriplasmin trials are summarised in the table below.

Summary of adverse events in trials TG-MV-007 and TG-MV-007 (Safety Set)

	TG-MV-006		TG-MV-007		Pooled
	Ocriplasmin n/N (N=220)	Placebo n/N (N=106)	Ocriplasmin n/N (N=245)	Placebo n/N (N=81)	RD (95%CI)
All AEs	182 (82.7)	77 (72.6)	176 (71.8)	52 (64.2)	**0.09 (0.02, 0.17)**
Ocular	163 (74.1)	65 (61.3)	162 (66.1)	42 (51.9)	**0.13 (0.05, 0.22)**
SE	159 (72.3)	62 (58.5)	159 (64.9)	38 (46.9)	**0.16 (0.07, 0.24)**
Drug-related AEs	93 (42.3)	21 (19.8)	93 (38.0)	19 (23.5)	**0.19 (0.11, 0.27)**
Ocular	93 (42.3)	21 (19.8)	93 (38.0)	19 (23.5)	**0.19 (0.11, 0.27)**
SE	93 (42.3)	21 (19.8)	93 (38.0)	19 (23.5)	**0.19 (0.11, 0.27)**
Serious AEs	32 (14.5)	13 (12.3)	33 (13.5)	11 (13.6)	0.01 (-0.05,0.07)
Ocular	22 (10.0)	11 (10.4)	15 (6.1)	9 (11.1)	-0.03 (-0.08,0.03)
SE	21 (9.5)	11 (10.4)	15 (6.1)	9 (11.1)	-0.03 (-0.08,0.02)
Severe AEs	29 (13.2)	7 (6.6)	13 (5.3)	7 (8.6)	0.02 (-0.08, 0.11)
Ocular	19 (8.6)	5 (4.7)	5 (2.0)	6 (7.4)	-0.01 (-0.10, 0.08)
SE	18 (8.2)	5 (4.7)	5 (2.0)	6 (7.4)	-0.01 (-0.10, 0.08)
Disc. due to AEs	2 (0.9)	2 (1.9)	2 0.8)	0 (0)	0.00 (-0.02, 0.02)
Death	3 (1.4)	0 (0)	1 (0.4)	0 (0)	0.01 (-0.01, 0.02)

Source: Table 36, p126 of the submission

6.19 The submission (p124) stated that the reported adverse events do not include adverse events following vitrectomy (if conducted). All drug-related adverse events were ocular in nature with the most common being vitreous floaters, eye pain, photopsia 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. Ocriplasmin was associated with significantly more total adverse events, drug-related adverse events and study-eye adverse events. The CSRs for Trials TG-MV-006 and TG-MV-007 stated that the 4 deaths in the ocriplasmin arms were considered unrelated to ocriplasmin (cerebral haemorrhage, two by lung cancer, and congestive heart failure). No additional safety concerns were noted in the assessment of extended harms.

6.20 The adverse events reported in the two vitrectomy trials are presented in the table below for comparison. The ESCs noted that these rates were not used in the modelled economic evaluation.

Summary of weighted average adverse events reported in the Ezra 2004 and VHMS vitrectomy trials

Adverse event	Cataract	Retinal detachment	Retinal tear	Vitreous haemorrhage	Elevated IOP
Weighted average of vitrectomy trials	48.91% (N=276)	4.63% (N=691)	13.75% (N=349)	3.23% (N=93)	5.43% (N=276)

Benefits/harms

6.21 The table below summarises the comparative benefits/harms of ocriplasmin and placebo based on the ITT (FAS) population in the trials.

Summary of comparative benefits and harms for ocriplasmin and placebo at Day 28 and ocriplasmin ± vitrectomy and placebo ± vitrectomy at Month 6

Trial	Ocriplasmin	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Ocriplasmin	Placebo	
Benefits						
Non-surgical VMA resolution at Day 28						
Pooled	123/464	19/188	**2.69 (1.44, 5.05)**	26.5	10.1	**0.17 (0.12, 0.23)**
VMA resolution at Month 6 (non-surgical or surgical) – source: Appendix F to the submission, Tables 43, 44 and 45						
Pooled	184/459	63/181	1.15 (0.92, 1.45)	40.1	34.8	0.05 (-0.03, 0.14)
VMA resolution at Month 6 (non-surgical or surgical) – source: Pre-ESC response, Table 4						
Pooled	*199/461*	*65/187*	*1.24 (0.99, 1.55)*	*43.2*	*34.8*	***0.08 (0.00, 0.17)***
Non-surgical FTMH closure resolution at Day 28						
Pooled	43/106	5/47	**3.84 (1.62, 9.08)**	40.6	10.6	**0.31 (0.18, 0.43)**
Non-surgical FTMH closure resolution at Month 6						
Pooled	43/106	8/47	**2.39 (1.22, 4.67)**	40.6	17.0	**0.25 (0.10, 0.39)**
FTHM closure resolution at Month 6 (non-surgical or surgical)						
Pooled	80/106	32/47	1.09 (0.76, 1.56)	75.5	68.1	0.07 (-0.19, 0.33)
≥2 lines improvement in best corrected visual acuity (BCVA) at Month 6						
Pooled	130/464	32/188	**1.66 (1.17, 2.35)**	28.0	17.0	**0.11 (0.04, 0.18)**
Vitrectomy required at Month 6						
Pooled	82/464 (17.7)	50/188 (26.6)	**0.68 (0.50, 0.93)**	17.7	26.6	**-0.08 (-0.16, -0.01)**

Trial	Ocriplasmin			Placebo			Mean difference (95% CI)
	n	Mean ∆ BVCA	SD	N	Mean ∆ BVCA	SD	
Mean change from baseline in BCVA letters at Day 28							
Pooled	464	2.6	NR	187	2.72	NR	-0.12 (-1.32, 1.09)
Mean change from baseline in BCVA letters at Month 6							
Pooled	464	3.55	NR	187	2.45	NR	1.11 (-0.64, 2.85)

Harms						
	Ocriplasmin	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Ocriplasmin	Placebo	
Any ocular events						
Pooled	325/465	107/187	**1.23 (1.07, 1.41)**	69.8	57.2	**0.13 (0.05, 0.22)**
Drug-related ocular events						
Pooled	186/465	40/187	**1.87 (1.39, 2.51)**	40.0	21.4	**0.19 (0.11, 0.27)**

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation

6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with ocriplasmin compared to placebo:

- approximately 17 additional patients would have non-surgical VMA resolution at Day 28;
- approximately 31 and 25 additional patients would have FTMH closure at Day 28 and Month 6, respectively;
- approximately 11 additional patients would have a ≥2 lines improvement in best corrected visual acuity (BCVA) at Month 6;
- approximately 8 fewer patients would have a vitrectomy by Month 6; and
- approximately 13 and 19 additional patients would have any ocular and a drug-related ocular adverse event, respectively.

No statistically significant differences in mean change of BVCA were observed between treatments at Day 28 or Month 6.

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

Clinical claim

6.23 The submission described ocriplasmin as being:

- superior in terms of comparative effectiveness and inferior in terms of comparative safety over watchful waiting (based on TG-MV-006 and TG-MV-007)
- inferior in terms of comparative effectiveness and superior in terms of comparative safety over vitrectomy (based on VMHS and Ezra 2004).

6.24 The ESCs considered that it is not clear whether ocriplasmin improves patient-relevant outcomes. Any effect on avoiding vitrectomy at six months appears to be numerically small, not clearly related to the primary surrogate outcome of non-surgical VMA resolution at 28 days, and may not be sustained beyond six months: i.e. ocriplasmin may postpone rather than replace vitrectomy. Similarly, any effect on improving BCVA is not supported by differences in mean change from baseline in BCVA letters, relies on selecting secondary results of differences in proportions of patients on either side of thresholds of changes in letters of BCVA from baseline at Month 6, and may not represent a clinically significant improvement in vision related quality of life.

6.25 The ESCs also considered that it is not clear whether there is any treatment effect variation according to particular subgroups. In relation to the prespecified subgroup of patients with a macular hole, it is possible that this may identify patients with more severely distorted vision at baseline who experience a greater absolute effect (with a lower NNT) rather than a greater relative effect.

6.26 The PBAC agreed with the ESCs that the effectiveness of ocriplasmin in improving patient-relevant outcomes is not clear.

6.27 The PBAC agreed that ocriplasmin is inferior in terms of comparative effectiveness and superior in terms of comparative safety over vitrectomy.

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

Economic analysis

6.28 The submission presented a modelled economic evaluation (CUA) based on no explicit claim for the scenario modelled (i.e., ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy).

6.29 The CUA generated a weighted average ICER of $15,000/QALY - $45,000/QALY across three subgroups based on VMA and MH resolution results using individual patient data from the trials, extrapolated to 28 years (from 6 months in the trial) and applying utility weights from multiple studies.

6.30 Rather than relying on the ITT results from the trials, the modelled economic evaluation was based on three independent subgroups of patients (i) VMT only, (ii) VMT + ERM and (iii) VMT + MH. The definition of these subgroups differed from the definitions used to identify the prespecified subgroups analysed in the trial reports. The modelled economic evaluation for these subgroups was based on individual patient data that were not provided with the submission. The ESCs noted that IPD results were provided with the PSCR. However, these data were not able to be independently evaluated, including determining how they contributed as inputs to the models for each subgroup.

6.31 For all subgroups in the base case, the opportunity to be treated with vitrectomy was restricted to a period of the first 2.25 years of the model, where the rate for surgery was assumed to be constant (albeit at a higher rate for those with MH compared with those without). The ESCs did not consider the assumption of a constant probability of undergoing vitrectomy to be appropriate as the probability may reasonably be a function of time with a higher rate being associated with a longer time of unresolved VMT and/or MH. The implications of this approach are summarised in the table below

VMT only	VMT + ERM	VMT + MH
The model included 1,000 patients in each cohort. Patients only had the opportunity to undergo a vitrectomy and transit to the "resolved" health state in monthly cycles of 1-5 of the short-term model and 3-monthly cycles of 0-7 in the long-term model (up to 2.25 years). Cycles 27-48 of the long-term model were annual. Consistent with the trial, no vitrectomies were performed in the first month of the model, and the submission justified this approach by stating that it emulated waiting lists.		
At 6 months in the model, 42.7% vs 22.1% of VMT only patients were in the "resolved" health state (i.e., have had success with ocriplasmin or have undergone vitrectomy) compared with 60.4% and 46.1% at 2.25 years (difference = 14.3%), for the ocriplasmin and comparator arms, respectively. At 2.25 years, 371 and 503 of the patients who were alive and who may have benefited from vitrectomy (which was assumed to resolve VMT in 100% of cases) in the ocriplasmin and comparator arms, respectively, were never treated and their VA was allowed to deteriorate over the remaining 26 years of the model.	At 6 months in the model, 20.5% vs 11.7% of VMT + ERM patients were in the "resolved" health state (i.e., have had success with ocriplasmin or have undergone vitrectomy) compared with 41.7% and 35.2% at 2.25 years (difference = 6.5%), for the ocriplasmin and comparator arms, respectively. At 2.25 years, 515 and 571 of the patients who were alive and who may have benefited from vitrectomy (which was assumed to resolve VMT in 100% of cases) in the ocriplasmin and comparator arms, respectively were never treated and their VA was allowed to deteriorate over the remaining 26 years of the model.	At 6 months in the model, 77.8% vs 68.7% of VMT + MH patients were in the "resolved" health state (i.e., have had success with ocriplasmin or have undergone vitrectomy) compared with 93.1% and 89.9% at 2.25 years (difference = 3.2%), for the ocriplasmin and comparator arms respectively. At 2.25 years, 3 and 5 of the patients who were alive and who may have benefited from vitrectomy (the first vitrectomy was assumed to resolve MH in 82.43% of cases) in the ocriplasmin and comparator arms, respectively were never treated and their VA was allowed to deteriorate over the remaining 26 years of the model.
VMT only was associated with better VA, with the majority of such patients (86.5%) in VA health states 1-3 (or 56-100 ETDRS letters of a possible 100 letters) at baseline in the trials.	VMT + ERM was associated with better VA, with the majority of such patients (82.5%) in VA health states 1-3 (or 56-100 ETDRS letters of a possible 100 letters) at baseline in the trials.	Macular holes were associated with poor VA, with the majority of such patients (83.5%) in VA health states 3-6 (or 0-65 ETDRS letters of a possible 100 letters) at baseline in the trials.
For unresolved VMT and/or MH, in each 3-month cycle in the long-term model, patients had a probability of 87.1% for staying in the same VA health state or a 12.9% probability of moving to a reduced VA health state. In each annual cycle in the long-term Markov model, patients had a probability of 57.5% for staying in the same VA health state or a 42.5% probability of moving to a worse VA health state.		
The implication of the lack of, or delay in, allowing treatment with vitrectomy in the comparator arm resulted in a greater proportion of patients experiencing deterioration in VA and subsequent decrements in quality of life. Assumptions allowing a greater proportion of patients to be treated with vitrectomy had a significant impact on the ICER.		

6.32 Whilst a period of watchful waiting was considered appropriate by the ESCs in patients with no MH, given the possibility of spontaneous resolution of VMT and the invasive nature of a vitrectomy, the lack of treatment of a significant proportion of the modelled population amongst those with VMT only or VMT + ERM did not appear justified given:

- the impact of VMT on visual acuity and visual disturbances and the possibility of progression to developing a MH; and
- the majority of patients enrolled in the trials forming the basis of the submission did not have a macular hole, yet the majority (>79%) were "expected to undergo vitrectomy (defined by a Yes/no answer for the question asked of the Investigator prior to randomisation: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy")".

Translation issues

6.33 The following tables summarise the overall approach and key comments with respect to critical assumptions applied in the model.

Application of trial data and extrapolation of visual acuity in non-study eye

	Description	Comment
Step 1	IPD from the trial was used to inform the starting distributions across the 6 visual acuity health states for the non-study eye in both arms.	• The starting visual acuity health state distributions were based on the trial population. Given the IPD results from the trial were not provided, there was a possibility that non-statistically significant differences may have been modelled.
Step 2	Extrapolation of lifetime visual acuity in the non-study eye. Transition probabilities to model visual decline at the rate of the "age-matched general public" were derived from Laitinen et al 2005 to model the 6 visual acuity health states over time.	• The decline of vision loss was assumed to be constant / linear over time.

Application of trial data and extrapolation of visual acuity in the study eye

	Description	Comment
Step 1	Short-term model (outcomes at 6 months) IPD, regression analyses and assumptions were used to inform a short-term decision tree model which was used to stratify the modelled cohort of study eyes between 6 disease-related health states (see Table C.0.2 of the commentary) and further sub-stratify into the 6 visual acuity health states (see Table C.0.1 of the commentary) within each of the disease-related health states. Spontaneous resolution of VMT and MH were accounted for in the short-term model based on the rates observed in IPD data.	• The structural approach adopted to model every clinical event and transition in the first 6 months using a mixture of IPD, ordered logit models and assumptions may not be reasonable as it added unnecessary complexity and non-transparency to the model. • The justification provided for such an approach appeared to be that there was insufficient trial data to inform across the 36 modelled health states (6 visual acuity x 6 disease related health states). This however was not a justification for adopting a highly complex model structure to begin with. • The submission did not provide the IPD results for the modelled subgroups, for trial outcomes at 6 months (i.e. vitrectomies, VMT resolutions, MH closures, distributions across visual acuity or disease-related health states) to allow an evaluation of how the model compared with trial data to 6 months. • Several issues were also identified during the evaluation with the derivation of the extensive transition probabilities in the short-term model, including the use of unconditional probabilities instead of conditional probabilities and inconsistencies between the presented results of the ordered logit models and those used in the model itself. • Given the IPD results from the trial were not provided, there was a possibility that non-statistically significant differences may have been modelled throughout the short-term decision tree across arms.

	Description	Comment
Step 2	VA at 6 months VA at baseline, month 1 and month 3 were derived from IPD from the trial. VA at month 6 was estimated from the distribution derived from the short-term model above. The distributions of visual acuity at month 2 and at month 4 and 5 were assumed to be linear changes from 1-3 or 3-6 months, respectively.	• The starting visual acuity health state distributions were based on the trial population. Non-statistically significant differences may have been modelled (see above). • The same issues as discussed above were applicable because the distribution of visual acuity at 6 months was derived from the decision-tree model.
Step 3	Long-term Markov model A long-term Markov model was used to extrapolate the results from the decision-tree beyond 6 months. - Transitions through the 6 disease-related health states were assumed to be possible for the first 8 cycles of the model (or 2.25 years overall). The rates of clinical events which drive the transitions between disease related health states were assumed to be constant and were based on the rate of events derived for the short-term decision model to 6 months and several assumptions. Spontaneous resolution of VMT or MH was not permitted. - Transitions through the 6 visual acuity health states within each of the 6 disease-related health states were driven by (i) the occurrence of clinical events, and (ii) whether or not VMT was resolved. The decline in visual acuity of resolved or unresolved VMT/MH health states was assumed to be constant, derived from Laitinen et al 2005 and Hikichi et al 1995, respectively. The change in visual acuity for clinical events was assumed once-off and derived from IPD from the trial.	• The rates used to inform transitions through the disease related health states were all assumed equivalent (and hence constant) to the rates in the 6 month short-term decision tree. This assumption may not be reasonable, particularly for the probability of having a vitrectomy since the probability may also reasonably be a function of time with a higher rate being associated with a longer time of unresolved VMT. • In addition, as a result of the assumption that clinical events can only occur for the first 8 cycles (2.25 years) and the constant transition rate to vitrectomy, a significant proportion of patients in the VMT subgroups who would benefit from a vitrectomy never received a vitrectomy in the model. This may not be reasonable and the **model is highly sensitive to the assumed number of patients who have undergone a vitrectomy for the VMT subgroups**.

Transformation of visual acuity in the non-study eye and study-eye

	Description	Comment
Step 1	The distributions across the 6 visual acuity health states for each cycle of the model in the non-study eye and study-eye were transformed to distributions across the 6 visual acuity health states in the "best-seeing-eye" and "worst-seeing-eye" through the construction of a series of compound probability formulas.	• This step may have been unnecessary given the VMT is predominately a unilateral condition, and the affected eye is typically the worst-seeing-eye.
Step 2	Mortality was introduced into the model, with differential mortality for the cohort who were (i) not blind, (ii) blind in one eye or (iii) blind in two eyes based on the constructed visual acuity distributions of the best and worst seeing eyes.	• The mortality rates applied for patients being blind in one eye or two eyes were higher than those previously considered by the PBAC. However, sensitivity analyses changing the **assumed vision-related mortality had very little impact on the ICERs.**
Step 3	A weighted average VA utility was estimated for each cycle, based on the proportion of alive patients in each VA health state for the non-study eye and study eye and a utility matrix constructed from Czoski-Murray et al 2009 (see Section C.3.2.1 of the commentary). The average utility each cycle was then applied to all alive patients in the transformed model of worst and best seeing eye.	• There was an error in the methodology of estimating the average utility associated with visual acuity because the model used to derive the average utility was based on the distribution across the visual acuity health states in the study eye and non-study eye which included only general mortality each cycle. Because the final distribution of visual acuity of best and worst seeing eye included differential mortality rates, the calculations were incorrect. Although this favoured ocriplasmin, the differences were small as it mainly affected later cycles in the model which were the most heavily discounted.
Step 4	Dis-utilities and costs were attributed to each clinical event and unresolved symptoms per cycle, which includes adverse events of ocriplasmin and vitrectomy.	• There was an error in the methodology for estimating the disutility for metamorphopsia associated with unresolved VMT as it was calculated using the distributions of the study and non-study eye but applied to the distributions of the best and worst seeing eye. Due to the differential mortality rates, a disutility was allocated to dead patients. Although favouring ocriplasmin as there were a greater number of deaths in the watchful waiting arm, the effect was minimal on the ICERs.
Step 5	The costs and utilities were discounted at an annual rate of 5% and summed to generate the ICER.	

Modelled evaluation

6.34 The model had two components: a short-term (6-month) decision tree and a long-term (28-year) extrapolation Markov model. The short-term decision tree covered the first 6 months of treatment, and was predominantly based on clinical trial data pooled from TG-MV-006 and TG-MV-007 IPD which was not provided in the submission. It had monthly cycles. The short-term decision tree determined the starting position of patients in the long-term extrapolation Markov model, which started at 6 months post-treatment and then had a lifetime time horizon. The Markov model applied 3-monthly cycles for the first 5 years and annual cycles thereafter. After 2.25 years patients in the model are no longer able to be treated with vitrectomy. The table below provides a summary of the model structure and rationale.

Summary of model structure and rationale

Time horizon	27.75 years in the model base case versus 0.5 years in trial (baseline age of the cohort was 72; modelled to 99.75 years of age)
Outcomes	QALYs
Methods used to generate results	Cohort expected value analysis
Cycle length	Short-term model: - one-month cycles (combined cycles 0 to 5) Long-term model: - three-month cycles (combined cycles 6 to 26) - annual cycles (combined cycles 27 to 48)
Transition probabilities	**Non-study-eye** Short- and long-term models Visual acuity health state transition probabilities (linear extrapolation of one-month cycles between the 3-month transitions in the short-term model): see Table C.2.1.4.1.1 of the commentary **Study-eye** Short-term model: linear extrapolation of visual acuity for months not directly reported in the trial data. Long-term model: decision-tree transition probabilities - "VMT only": see Table C.1.4.2.3 and C.1.4.3 of the commentary - "VMT + ERM": see Table C.1.4.2.4 and C.1.4.3 of the commentary - "VMT + MH": see Table C.1.4.2.5 and C.1.4.3 of the commentary disease-related health state transition probabilities: see Tables C.2.1.1 and C.0.3 of the commentary visual acuity health state transition probabilities: see Tables C.2.1.4.1.1, C.2.1.4.2.1, C.2.1.4.3.1, and C.0.3 of the commentary **Best-seeing-eye / worst-seeing-eye** Conditional probabilities: see Table C.3.1 of the commentary Mortality rates: see Attachment D of the commentary
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: constructed during the evaluation

6.35 The ESCs considered that the model presented in the submission was overly complex with multiple components and health states. In addition, the multiple stages applied across the model and the links between them were inadequately supported. These stages included moving: from a short-term decision tree to a long-term Markov model for extrapolation; from study/non-study eye basis to a best/worst seeing eye basis; and from subgroups based on results, which may not represent meaningful differences, to a weighted average overall ICER.

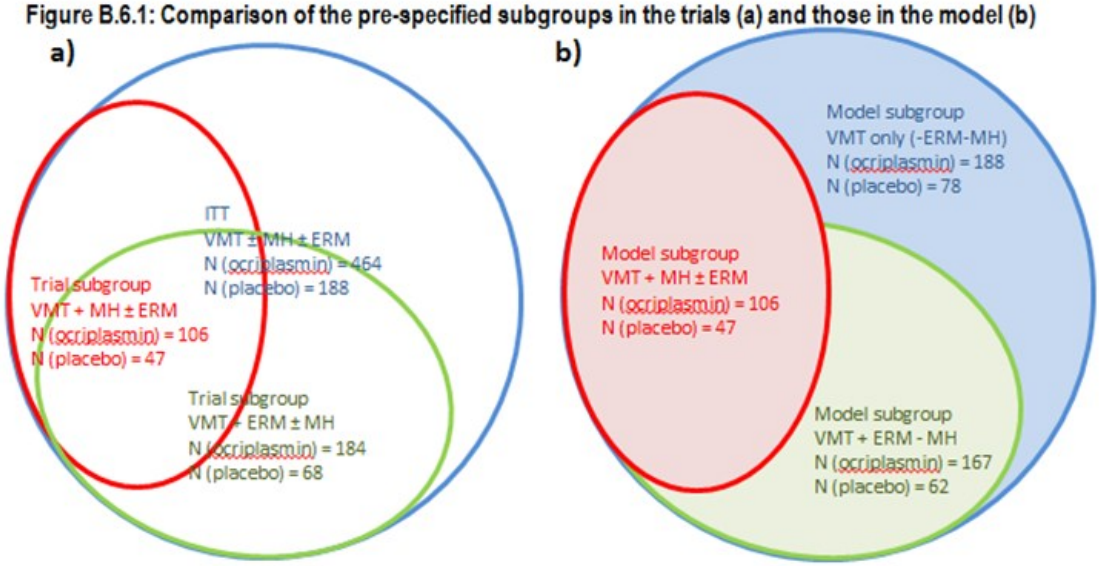
6.36 The PBAC noted the advice of the ESCs that, as the model moves across each of its stages, there were implicit assumptions which either could not be verified (e.g. the translation between the numbers of resolved patients for the study/non-study eye basis to the numbers of patients alive for the best/worst seeing eye) or could be shown to be uncertain (e.g. the reliance on subgroup results rather than ITT results), so the complexity of the model structure, even if the logic can be followed, added to, rather than reduced, uncertainty. As the majority of 'study eyes' are the worse seeing eye, it was difficult to understand the need for this particular complexity. Further, the validity of transition probabilities between different health states and

across different stages of the model could not be verified with respect to the subsequently provided IPD results for these subgroups. Therefore, the ESCs advised that, as constructed, the model did not form a suitable basis for PBAC consideration.

6.37 The PBAC clarified that the subgroups defined for the model did not match the subgroups prespecified for the trial analyses, as illustrated by the table and the figure below.

Prespecified subgroups in the trials	Subgroups modelled in the economic evaluation
VMT + FTMH ± ERM	VMT + FTMH ± ERM (ie, prespecified)
VMT + ERM ± FTMH	VMT + ERM with **NO MH** (ie, not prespecified)
	VMT only **(NO MH, NO ERM)** (ie, not prespecified)

Figure B.6.1: Comparison of the pre-specified subgroups in the trials (a) and those in the model (b)



Source: constructed during the evaluation

6.38 The results of the trial based and modelled economic evaluation are presented below.

Results of the economic evaluation

Step	OCRI	WW	Increment
Step 1: Trial-based % VMT-resolution at Day 28 (all subgroups); ocriplasmin cost + modelled incremental costs at 6-months. Cost to 6 months per additional VMT resolution at day 28.			
Costs (OCRI costs only)	[redacted]	[redacted]	[redacted]
Cost (model costs to 6mths, incl. OCRI)[a]	[redacted]	[redacted]	[redacted]
% VMT resolution (day 28)	26.5%	10.1%	15.4%
Incremental cost (OCRI costs only) /extra VMT resolution (day 28)			[redacted]
Incremental cost (model costs to 6mths, incl. OCRI) / extra VMT resolution (day 28)			[redacted]
Step 2: Trial-based % MH closure at 6 months ("VMT + MH" subgroup); ocriplasmin cost + modelled incremental costs at 6-months. Cost to 6 months per additional MH closure at 6 months.			
Costs (OCRI costs only)	[redacted]	[redacted]	[redacted]
Cost (model costs to 6mths, incl. OCRI) (VMT + MH subgroup)	[redacted]	[redacted]	[redacted]
% MH closure (6 months) (VMT + MH subgroup)	40.6%	17%	23.6%
Incremental cost (OCRI costs only) /extra MH closure (6 months) (VMT + MH subgroup)			[redacted]
Incremental cost (model costs to 6mths, incl. OCRI) / extra MH closure (6 months) (VMT + MH subgroup)			[redacted]
Step 3: Trial based % with at least a 1 line improvement in BCVA at 6 months (all subgroups); ocriplasmin cost + modelled incremental costs at 6-months. Cost to 6 months per additional person with at least a 1 line improvement in BCVA at 6 months.			
Costs (OCRI costs only)	[redacted]	[redacted]	[redacted]
Cost (model costs to 6mths, incl. OCRI)[a]	[redacted]	[redacted]	[redacted]
% with at least a 1 line improvement in BCVA (6 months)	44.2%	38.3%	5.9%
Incremental cost (OCRI costs only) /extra at least a 1 line improvement in BCVA (6 months)			[redacted]
Incremental cost (model costs to 6mths, incl. OCRI) / extra at least a 1 line improvement in BCVA (6 months)			[redacted]
Step 4: Trial based % with at least a 2 line improvement in BCVA at 6 months (all subgroups); ocriplasmin cost + modelled incremental costs at 6-months. Cost to 6 months per additional person with at least a 2 line improvement in BCVA at 6 months.			
Costs (OCRI costs only)	[redacted]	[redacted]	[redacted]
Cost (model costs to 6mths, incl. OCRI)[a]	[redacted]	[redacted]	[redacted]
% with at least a 2 line improvement in BCVA (6 months)	28.0%	17.0%	11.0%
Incremental cost (OCRI costs only) /extra at least a 2 line improvement in BCVA (6 months)			[redacted]
Incremental cost (model costs to 6mths, incl. OCRI) / extra at least a 2 line improvement in BCVA (6 months)			[redacted]
Step 5a: Modelled economic evaluation (to 6 months); an ICER in terms of costs per additional QALY			
Costs (model costs to 6mths, incl. OCRI)	[redacted]	[redacted]	[redacted]
LYs gained	[redacted]	[redacted]	[redacted]
QALYs gained	[redacted]	[redacted]	[redacted]
Incremental cost (model costs to 6mths, incl. OCRI) / extra LY gained (6 months)			**NE[b]**
Incremental cost (model costs to 6mths, incl. OCRI) / extra QALY gained (6 month)			[redacted] / **QALY**

[a] weighting done post-subgroup-models; as the exact weights are not reported, the results were weighted during the evaluation assuming the following: VMT only=266/648 (41.05%); VMT + ERM=229/648 (35.34%); VMT + MH=153/648 (23.61%)

[b] death is not modelled within the first 6months, therefore there is no incremental change in life-years to 6 months; and an ICER cannot be estimated

Source: Table 175, p391 of the submission

Results of the economic evaluation

	"VMT only"			"VMT + ERM"			"VMT + MH"		
	OCRI	WW	Incr.	OCRI	WW	Incr.	OCRI	WW	Incr.
Step 5b: Modelled economic evaluation (life-time); an ICER in terms of costs per additional QALY									
Costs	[redacted]								
Life Years	[redacted]								
QALYs	[redacted]								
Incr. cost/ LY	**[redacted] / LY**			**[redacted] / LY**			**[redacted] / LY**		
Incr. cost/ QALY	**[redacted] / QALY**			**[redacted] / QALY**			**[redacted] / QALY**		
							TOTAL[a]		
							OCRI	**WW**	**Incr.**
Costs							[redacted]		
LYs gained							[redacted]		
QALYs gained							[redacted]		
Incremental cost/extra LY gained							**[redacted] / LY**		
Incremental cost/extra QALY gained							**[redacted] / QALY**		

[a] weighting done post-subgroup-models; as the exact weights are not reported, the results were weighted during the evaluation assuming the following: VMT only=266/648 (41.05%); VMT + ERM=229/648 (35.34%); VMT + MH=153/648 (23.61%)

Source: Table 175, p391 of the submission

6.39 The ESCs considered that the plausibility of this ICER would need to be assessed in that:

- there was uncertainty that the three subgroups represent clinically relevant groups to justify the independent modelling of each;
- differences between the treatment arms over the time horizon of the model were driven by the proportion of patients in each disease-related health state and the visual acuity health states embedded within them derived from the IPD up to 6 months in the trials, and that statistically significant differences between the treatment arms of the subgroups had not been established; and
- too few patients in the VMT only and VMT + ERM subgroups were appropriately treated in a timely manner, given the comparison of

  ocriplasmin ± vitrectomy and watchful waiting ± vitrectomy

with the model assuming VMA resolution was 100% for vitrectomy and the reported VMA resolution rate for the ITT population was 17% at 28 days for ocriplasmin (compared with placebo), and with similar costs ($5,376.94 for vitrectomy versus $[redacted] for ocriplasmin), and treatment with ocriplasmin did not preclude subsequent vitrectomy surgery.

6.40 The ESCs also questioned the plausibility of assuming that vitrectomy was no longer an option after two years, yet visual acuity still deteriorated to blindness without further intervention. In addition, the trial report noted that 80% of patients were anticipated to have vitrectomy, but the model only allowed fewer than 50% to have vitrectomy. This was important because the model assumed 17% resolved at 28 days after ocriplasmin compared to 100% resolved after vitrectomy, the costs of a vitrectomy procedure and an ocriplasmin administration were similar, and the use of ocriplasmin did not preclude subsequent vitrectomy.

6.41 The stepped economic evaluation showed that moving from Step 5a (a trial-based economic evaluation without any significant differences across arms of the model and an ICER/QALY of more than $200,000/QALY) to Step 5b (an extrapolated model

with a significant lifetime difference in both incremental life-years gained and incremental QALYs and an ICER/QALY of $15,000/QALY - $45,000/QALY) resulted in substantial changes to the estimated ICER/QALY. The main drivers for the reduction in ICER/QALY were a manufactured difference in the proportion resolved across the arms of the model for each of the subgroups (for example, in the "VMT only" subgroup, the proportion resolved/cured for ocriplasmin increased from 39% to 42% and the proportion resolved/cured for the comparator decreased from 29% to 22%), and a constant rate assumption in the long-term model which accrued incremental gains in both quantity and quality of life benefits extrapolated over the residual life expectancy of the cohorts.

6.42 The results of the sensitivity analyses indicated that the model was most sensitive to the i) time horizon, ii) the rate of visual acuity decline for unresolved VMT, iii) the assumption that spontaneous resolution of VMT or MH is not possible post 6 months, and iv) the assumptions made regarding subsequent treatment after 2 years.

6.43 Overall the ESCs considered that the ICERs could not be relied upon because of the level of the complexity and the lack of transparency of the model presented.

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

Drug cost: $[redacted] per eye per lifetime.

Estimated PBS usage & financial implications

6.44 The submission was considered by the Drug Utilisation Sub-Committee (DUSC). The DUSC considered the approach taken by the sponsor to estimate utilisation to be broadly reasonable, however many of the figures, assumptions and calculations were incorrect or could not be verified. Some of those were:

- The estimated percent of vitrectomies for vitreomacular traction of 2.1% could not be verified. DUSC suggested the correct value should be 1.6%.
- The percent of patients who received a vitrectomy of 7.8% could not be verified. DUSC suggested the correct value should be 16.3%.
- Therefore the calculated incidence of vitreomacular traction without macular holes was incorrect. DUSC suggested the correct value should be 6 eyes per 100,000 people.
- The estimation of the incidence of macular holes (8.8 eyes/100,000 people) could not be verified, but may be reasonable.
- The proportion of patients who avoid vitrectomy due to treatment with ocriplasmin could not be verified.

The DUSC considered the overall utilisation estimates were sensitive to these assumptions.

6.45 The DUSC considered the main utilisation issues were:

- Notwithstanding the issues of verification, there was limited data available of the incidence and prevalence of this condition.
- The submission overestimated incidence (as above) and underestimated uptake in eligible patients:
  - The adjustment for patients with macular holes that are ≤400 μm and associated with vitreomacular traction and would be eligible for ocriplasmin should possibly be lower than 74% in the first year of listing.

  - The uptake rates were likely substantially underestimated and it is unlikely that the uptake would be different in patients with or without macular holes or epiretinal membranes. Patients are likely to be treated when they are diagnosed, as clinicians are familiar with intraocular injections. As an intraocular injection is comparatively less invasive than a vitrectomy, it is likely patients would be willing to attempt treatment with ocriplasmin before undergoing a vitrectomy.
- There was considerable scope for leakage of ocriplasmin:
  - In patients with asymptomatic vitreomacular adhesion, which can be diagnosed using OCT. The restriction could include a test of visual acuity to align with the clinical trial population and reduce the potential for asymptomatic patients being treated.
  - In patients with macular holes larger than 400µm, particularly given it is a once-off administration, it may be trialled before vitrectomy.
- Multiple OCT tests may be administered to determine eligibility during periods of watchful waiting. The submission used the number of ocriplasmin treatments to estimate the use of OCT, which implicitly assumed no one who receives an OCT test would be ineligible for ocriplasmin.

6.46 The estimated PBS usage and financial implications are presented in the table below.

Estimated PBS usage & financial implications

	2014	2015	2016	2017	2018
Eligible population					
VMT only	[redacted]				
VMT + ERM	[redacted]				
VMT + MH	[redacted]				
Estimated number of patients / year (= scripts / year)					
VMT only	[redacted]				
VMT + ERM	[redacted]				
VMT + MH	[redacted]				
Cost to PBS/RPBS (less copayment)					
VMT only	[redacted]				
VMT + ERM	[redacted]				
VMT + MH	[redacted]				
Net financial implications of OCT / ocriplasmin to the MBS/PBS/RPBS					
OCT cost to MBS (85% benefit)	[redacted]				
Administration cost to MBS (85% benefit)	[redacted]				
Ocriplasmin cost to PBS/RPBS (less copayment)	[redacted]				
Cost offsets to government health budgets arising from avoiding vitrectomies and cataract surgeries					
Total offset	[redacted]				
Net cost of OCT / ocriplasmin to the Australian healthcare budget					
Total cost	[redacted]				

The redacted table above shows that at Year 5, the estimated total number of patients treated with ocriplasmin would be less than 10,000 and the total net cost to the Australian healthcare budget would be less than $10 million.

6.47 The DUSC considered the estimated PBS usage and financial implications were unlikely to be reliable as many of the figures, assumptions and calculations were incorrect or could not be verified and the overall utilisation was sensitive to those assumptions.

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

7 PBAC outcome

7.1 The PBAC rejected the submission to list ocriplasmin for the treatment of vitreomacular traction (VMT) including those with full-thickness macular hole (FTMH) 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. The PBAC accepted the ESCs advice that the modelled evaluation did not provide a suitable basis for decision-making.

7.2 The PBAC noted the requested PBS population was largely consistent with the populations enrolled in the randomised trials presented (TG-MV-006 and TG-MV-007). However, some exclusion criteria, such as vision acuity threshold and comorbidities, particularly age-related macular degeneration, were not included in the requested restriction.

7.3 The submission proposed ocriplasmin may replace vitrectomy in a proportion of patients with VMT and the PBAC considered this to represent an area of clinical need. However, the PBAC considered ocriplasmin may postpone vitrectomy rather than replace vitrectomy because, in the trials presented, 13-20% of patients who had successful non-surgical VMA resolution after the treatment with ocriplasmin would have to receive vitrectomy by Month 6. Thus the PBAC considered that the clinical place of ocriplasmin was not clear.

7.4 The PBAC agreed with the ESCs that the comparator was best described as ocriplasmin ± vitrectomy versus watchful waiting ± vitrectomy because this comparison was modelled for economic analysis. Although the submission also presented an indirect comparison of ocriplasmin and vitrectomy, the PBAC noted these results were not used in the modelled evaluation.

7.5 The PBAC noted that the two randomised trials compared ocriplasmin with placebo (watchful waiting), and allowed participants in both treatment arms to proceed to vitrectomy if symptoms deteriorated or failed to improve after four weeks. Although the ITT analysis showed that there were 8% fewer vitrectomies at Month 6 in the ocriplasmin arm than placebo, the PBAC noted that successful non-surgical VMA resolution at Day 28 did not appear to reliably predict avoidance of vitrectomy by the end of the trial. About 20% and 13% of patients receiving ocriplasmin in TG-MV-006 and TG-MV-007 respectively subsequently required a vitrectomy irrespective of whether this primary outcome was met. The PBAC also noted there were no differences in mean change from baseline in BCVA letters between ocriplasmin and placebo arms in both Day 28 and Month 6. The results for the vision-specific VFQ-25 quality of life instrument, which has a minimal clinically important difference (MCID) of 3.6, were equivocal, with a statistically significant pooled mean difference at 6

months less than this MCID (2.79; 95% CI: 0.91, 4.68) and a numerical difference in the proportions of patients with a >3.6 improvement (36% following ocriplasmin and 23% following placebo). Overall, the PBAC considered that 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 in the long-term.

7.6 The PBAC noted 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.

7.7 The trials (TG-MV-006 and TG-MV-007) reported ITT results and results from prespecified subgroups. However, the subgroups modelled in the economic evaluation appeared to differ from those prespecified for the trials. The PBAC considered the justification for the set of subgroups modelled in the evaluation to be unclear, and noted that multiple definitions of subgroups increases the extent of both chance and bias affecting the interpretation of the results for the subgroups presented.

7.8 The submission claimed ocriplasmin is superior in effectiveness and inferior in safety compared with watchful waiting. The submission also claimed ocriplasmin is inferior in effectiveness and superior in safety compared with vitrectomy. The PBAC accepted these claims but the PBAC considered that it is 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. Thus the PBAC considered that the clinical value of ocriplasmin was not clear.

7.9 The PBAC agreed with the ESCs that: 1) the structure of the model presented in the submission was overly complex, with multiple components and health states relying on assumptions that could not be verified or were uncertain, particularly regarding the projected differences in numbers, outcomes and costs of vitrectomy across the arms of the model; 2) it was uncertain whether subgroups defined for modelling in the economic evaluation were clinically relevant and plausible subgroups, with meaningful estimates of the effectiveness of ocriplasmin; 3) the trial data reported for the ITT populations were not those that were applied in the modelled economic evaluation; and 4) as constructed, the model did not form a suitable basis for PBAC consideration. The PBAC also noted that: 1) the projected transitions in the model could not be assessed due to the paucity of data presented on the natural history of the ocular condition; and 2) the PBAC has previously considered the Czoski-Murray et al 2009 source of utilities to have overestimated the difference between visual acuity defined health states in other ocular conditions.

7.10 The PBAC noted the ICER varied from more than $200,000/QALY at 6 months to about $15,000/QALY - $45,000/QALY over a lifetime (17 years). The PBAC considered the ICER was not informative because of the concerns about the model mentioned above. The PBAC considered a simpler model structure with better justified assumptions would likely be more informative for decision making.

7.11 The PBAC agreed with the DUSC that the utilisation estimates were unreliable as many of the figures, assumptions and calculations were incorrect or could not be verified.

7.12 Any future re-submission for ocriplasmin should take the form of a major submission.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Alcon is committed to working with the PBAC to secure reimbursement of ocriplasmin for patient benefit.