

Ocriplasmin for treating vitreomacular traction

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1 Guidance

1.1 Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if:

- an epiretinal membrane is not present
and
- they have a stage II full-thickness macular hole with a diameter of 400 micrometres or less **and/or**
- they have severe symptoms.

2 The technology

- 2.1 Ocriplasmin (Jetrea, ThromboGenics) is a truncated form of human plasmin, manufactured using recombinant DNA technology. It is 'indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole (MH) of diameter less than or equal to 400 microns'. It is administered by intravitreal injection at a dose of 0.125 mg. Repeated injections into the same eye are not recommended.
- 2.2 The summary of product characteristics lists the following adverse reactions for ocriplasmin: vitreous floaters, eye pain, photopsia, and conjunctival haemorrhage resulting from the injection procedure. Most of these reactions were non-serious, mild in intensity and resolved within 2 to 3 weeks. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The cost of an ocriplasmin injection is £2500 (excluding VAT) (0.5 mg in 0.2 ml solution; MIMS, July 2013). Because repeat injections are not recommended, this is the cost for a full course of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([section 7](#)) considered evidence submitted by the manufacturer of ocriplasmin and a review of this submission by the Evidence Review Group (ERG; [section 8](#)).

Clinical effectiveness

Background to the clinical evidence

- 3.1 The manufacturer's systematic literature review identified 2 randomised controlled trials that were relevant to the decision problem: TG-MV-006 and TG-MV-007. The data from these trials were assessed individually and as an integrated dataset. Three non-randomised controlled trials (TG-MV-001, TG-MV-008 and TG-MV-010) provided relevant safety and pharmacokinetic data.
- 3.2 TG-MV-006 was a randomised, placebo-controlled, double-blind trial conducted in the USA. People with vitreomacular traction were randomised to receive either a single injection of ocriplasmin (n=219), or a placebo injection of saline (n=107), and were followed up over 6 months. Inclusion criteria included a best corrected visual acuity (BCVA) of 20/25 or worse in the study eye, and 20/800 or better in the non-study eye. Exclusion criteria included a macular hole larger than 400 micrometres and previous vitrectomy in the study eye. At baseline 27.3% had a full-thickness (stage II) macular hole, 72.7% had vitreomacular traction (which could include a stage I macular hole), 37.1% had an epiretinal membrane, and 79.4% had an expected need for a vitrectomy. The mean BCVA score at baseline was 64.8 (standard deviation 10.53).
- 3.3 TG-MV-007 was a randomised, placebo-controlled, double-blind trial conducted in the USA and Europe (including the UK). People with vitreomacular traction were randomised to receive either a single injection of ocriplasmin (n=245), or a placebo injection of saline (n=81), and were followed up over 6 months. Inclusion criteria included a BCVA of 20/25 or worse in the study eye and 20/800 or better in the non-study eye. Exclusion criteria included a macular hole larger than 400 micrometres and previous vitrectomy in the study eye. At baseline, 19.6% had a full-thickness (stage II) macular hole,

80.4% had vitreomacular traction (which could include a stage I macular hole), 40.2% had an epiretinal membrane, and 88.7% had an expected need for a vitrectomy. The mean BCVA score at baseline was 63.8 (standard deviation 13.20).

- 3.4 The primary outcome of TG-MV-006 and TG-MV-007 was the proportion of patients with non-surgical resolution of focal vitreomacular adhesion at day 28 post-injection, as determined by masked central reading centre optical coherence tomography (OCT) evaluation. Secondary outcomes included the proportion of patients with total posterior vitreous detachment (PVD) at day 28, proportion of full-thickness (stage II) macular holes that closed without vitrectomy, proportion of patients not needing vitrectomy, an improvement of at least 2 or 3 lines in BCVA without need for vitrectomy, improvement in mean BCVA, and improvement in the 25-item Visual Function Questionnaire (VFQ-25). Safety outcomes included adverse events, with special attention to ocular events, such as worsening visual acuity (VA), worsening macular oedema, vitreous haemorrhage, retinal tear, retinal detachment, increase in ocular inflammation and intraocular pressure increases.

Clinical trial results

- 3.5 The manufacturer presented the whole population results from TG-MV-006 and TG-MV-007 (see 3.6), as well as the following subgroups:
- VMT without ERM (vitreomacular traction without an epiretinal membrane); this included people with a stage I macular hole (see 3.7)
 - VMT with ERM (vitreomacular traction with an epiretinal membrane); this included people with a stage I macular hole (see 3.8)
 - VMT with MH (vitreomacular traction with a stage II macular hole); this included people with an epiretinal membrane (see 3.9).
- 3.6 Data from both the clinical trials and the integrated analyses were presented for the whole population. The proportion of patients with vitreomacular traction resolution was statistically significantly greater in the ocriplasmin arm than the placebo arm for both trials and in the integrated analyses for the whole population (TG-MV-006: 27.9% and 13.1% respectively, 95% confidence

interval [CI] 6.0 to 23.5, $p=0.003$; TG-MV-007: 25.3% and 6.2% respectively, 95% CI 11.6 to 26.7, $p<0.001$; integrated analysis: 26.5% and 10.1% respectively, 95% CI 10.5 to 22.3, $p<0.001$). The proportion of patients with total PVD by day 28 was statistically significantly greater in the ocriplasmin than the placebo arm for both trials in the whole population (TG-MV-006: 16.4% and 6.5% respectively, 95% CI 3.1 to 16.7, $p=0.0014$; TG-MV-007: 10.6% and 0% respectively, 95% CI 6.8 to 14.5, $p<0.001$).

- 3.7 The manufacturer presented data on the VMT without ERM subgroup. The integrated analyses showed that the proportion of patients with vitreomacular traction resolution or total PVD by day 28 was statistically significantly greater in the ocriplasmin arm than the placebo arm (vitreomacular traction resolution: placebo 7.7%, ocriplasmin 29.8%, $p<0.001$; total PVD: placebo 2.6%, ocriplasmin 17.0%, $p<0.001$). Further secondary outcomes did not show a statistically significant difference between the treatment arms but did favour ocriplasmin (proportion of patients who received a vitrectomy by month 6: placebo 15.4%, ocriplasmin 8.0%, $p=0.091$; mean change in VA from baseline at day 28: placebo 2.5 letters, ocriplasmin 2.6 letters, $p=0.890$; mean change in VA from baseline at month 6: placebo 2.8 letters, ocriplasmin 3.1 letters, $p=0.728$). At month 6 more patients treated with ocriplasmin than placebo had gained letters, on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale (at least 10 letters gained: placebo 15.4%, ocriplasmin 25.5%, $p=0.051$; at least 15 letters gained: placebo 5.1%, ocriplasmin 10.1%, $p=0.140$). However, more patients treated with ocriplasmin had lost letters (at least 10 letters lost: placebo 3.8%, ocriplasmin 6.9%, $p=0.381$; at least 15 letters lost: placebo 1.3%, ocriplasmin 5.9%, $p=0.121$).
- 3.8 The manufacturer presented data on the VMT with ERM subgroup. The integrated analyses showed that there was no statistically significant difference between the placebo and ocriplasmin arm for any of the outcomes, and that the differences were small (proportion of patients with vitreomacular traction resolution by day 28: placebo 1.6%, ocriplasmin 7.8%, $p=0.085$; proportion of patients with total PVD by day 28: placebo 1.6%, ocriplasmin 3.6%, $p=0.444$; proportion of patients who received a vitrectomy by month 6: placebo 17.5%, ocriplasmin 11.4%, $p=0.231$; mean change in VA from baseline at day 28: placebo 2.7 letters, ocriplasmin 1.9 letters, $p=0.325$; mean change in VA from

baseline at month 6: placebo 2.3 letters, ocriplasmin 2.0 letters $p=0.685$). At month 6 more patients treated with ocriplasmin than placebo had gained letters. However, more patients treated with ocriplasmin had lost letters (at least 10 letters gained: placebo 9.5%, ocriplasmin 20.5%, $p=0.058$; at least 15 letters gained: placebo 3.2%, ocriplasmin 4.8%, $p=0.625$; at least 10 letters lost: placebo 1.6%, ocriplasmin 8.4%, $p=0.052$; at least 15 letters lost: placebo 0%, ocriplasmin 4.8%, $p=0.069$).

- 3.9 The manufacturer presented data on the VMT with MH subgroup. The integrated analyses showed that the proportions of patients with vitreomacular traction resolution, total PVD or macular hole closure without vitrectomy by day 28, or macular hole closure without vitrectomy by month 6, were statistically significantly greater in the ocriplasmin arm than the placebo arm (vitreomacular traction resolution: placebo 25.5%, ocriplasmin 50.0%, $p=0.006$; total PVD: placebo 8.5%, ocriplasmin 22.6%, $p=0.033$; macular hole closure at day 28: placebo 10.6%, ocriplasmin 40.6%, $p<0.001$; macular hole closure at month 6: placebo 17.0%, ocriplasmin 40.6%, $p<0.001$). Further secondary outcomes did not show a statistically significant difference between the treatment arms but did favour ocriplasmin (proportion of patients who received vitrectomy by month 6: placebo 57.4%, ocriplasmin 44.3%, $p=0.157$; mean change in VA from baseline at day 28: placebo 3.0 letters, ocriplasmin 3.9 letters, $p=0.691$; mean change in VA from baseline at month 6: placebo 2.3 letters, ocriplasmin 6.8 letters, $p=0.126$). At month 6, the proportion of patients gaining letters and patients losing letters favoured ocriplasmin (at least 10 letters gained: placebo 30.4%, ocriplasmin 44.3%, $p=0.104$; at least 15 letters gained: placebo 13.0%, ocriplasmin 27.4%, $p=0.063$; at least 10 letters lost: placebo 15.2%, ocriplasmin 8.5%, $p=0.233$; at least 15 letters lost: placebo 10.9%, ocriplasmin 6.6%, $p=0.421$).

Health-related quality-of-life results

- 3.10 Health-related quality-of-life data were collected during the TG-MV-006 and TG-MV-007 trials using the VFQ-25. The VFQ-25 has 12 subscales that measure the influence of visual disability and visual symptoms on generic health domains such as emotional wellbeing, social functioning, sense of independence, and other task-oriented domains related to daily visual functioning (such as driving). The manufacturer presented the integrated

analyses of these data for the whole population. In the ocriplasmin group, mean increases (representing improvements) were observed across all of the subscale and composite scores at month 6, and were numerically better than the placebo arm. A clinically meaningful improvement in the VFQ-25 composite score (minimum clinically important difference: 3.6) was observed in a significantly larger proportion of the ocriplasmin group (35.9%) than the placebo group (22.7%, $p=0.0016$). The mean change from baseline in VFQ-25 composite score at 6 months was significantly greater in the ocriplasmin group (3.4) than the placebo group (0.7, $p=0.007$). The general vision subscale score improved more in the ocriplasmin group than the placebo group (placebo 2.1, ocriplasmin 6.1, $p=0.024$). This score was affected by the primary efficacy outcome (vitreomacular adhesion resolution): in the ocriplasmin group, mean improvement from baseline in the general vision subscale score was 8.4 for patients who had vitreomacular adhesion resolution, and 5.3 for those who did not. The mean improvement from baseline in the composite score was 5.7 among patients who had vitreomacular adhesion resolution and 2.6 for those who did not. The manufacturer presented a meta-analysis that showed statistically significant improvements in VFQ-25 outcomes (expressed as a difference in means) with ocriplasmin in general vision, distance activities, dependency, and composite scores.

Adverse events of treatment

- 3.11 The manufacturer presented pooled adverse event data from 7 clinical trials because TG-MV-006 and TG-MV-007 were not powered to detect significant differences in treatment-related adverse events. The pooled trials were TG-MV-001, TG-MV-002, TG-MV-003, TG-MV-004, TG-MV-006, TG-MV-007 and TG-MV-010. The adverse events were mainly ocular events. The incidence of serious adverse events was similar between placebo (TG-MV-006 and TG-MV-007 12.8%, all studies 13.8%) and ocriplasmin (TG-MV-006 and TG-MV-007 13.3%, all studies 13.5%). The only suspected adverse drug reaction that appeared to be dose dependent was vitreous floaters. The most common serious adverse event reported in the study eye was macular hole, which was less common in the ocriplasmin group than in the placebo group (4.7% and 6.5% respectively in all studies combined). The manufacturer stated that most adverse events were non-serious, mild in intensity, and resolved, and therefore were not considered to be clinically significant.

Cost effectiveness

- 3.12 The cost-effectiveness evidence presented by the manufacturer consisted of a systematic literature review and a de novo model. The literature review was to identify all existing studies of the cost effectiveness of any intervention in patients with vitreomacular traction (including vitreomacular traction associated with a macular hole or epiretinal membrane). The systematic review did not identify any relevant cost-effectiveness studies, so the manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of ocriclasmin compared with 'watch and wait' in patients with VMT with ERM, VMT without ERM, and VMT with MH.

Model structure

- 3.13 The manufacturer's model had 2 components: a short-term decision tree and a long-term 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. 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 2–5 years. After 2 years (or 5 years in the sensitivity analysis) annual cycles were used, therefore assuming events such as vitrectomy and spontaneous resolution would occur before this.
- 3.14 The manufacturer's model covered the population stated in the scope and the marketing authorisation (that is, adults with vitreomacular traction, including when associated with macular hole of diameter less than or equal to 400 microns). However, the manufacturer modelled 3 different subgroups of this population, which were defined by baseline characteristics: VMT without ERM, VMT with ERM (the VMT subgroups included patients with stage I macular holes), and VMT with MH (macular holes were stage II; this group included people with an epiretinal membrane). There were 2 short-term decision tree models used, one for the VMT with MH group and one for the other 2 subgroups. The structure of the long-term extrapolation Markov model was the same for all 3 subgroups. The manufacturer's short-term decision tree

for patients with VMT (with or without ERM) had the following decision nodes: non-surgical vitreomacular traction resolution (at day 28 or month 6), visual acuity health state 1–6 (see 3.15), vitrectomy, macular hole at month 6. The manufacturer's short-term decision tree for patients with VMT with MH had the following decision nodes: non-surgical macular hole resolution (at day 28 or month 6), vitrectomy (first or second), macular hole closed, non-surgical vitreomacular traction resolution at month 6. The manufacturer assumed that macular hole closure would lead to vitreomacular traction resolution. Patients finished the decision tree in 1 of 6 different health states, which were in the long-term Markov model. These health states were: resolved (vitreomacular traction and macular hole), vitreomacular traction unresolved without macular hole, vitreomacular traction unresolved with macular hole, vitreomacular traction resolved with macular hole (no vitrectomies), vitreomacular traction resolved with macular hole (1 vitrectomy) or vitreomacular traction resolved with macular hole (2 vitrectomies). The manufacturer's long-term Markov model also had a 'death' state. Patients transitioned to another health state as a result of the following events: spontaneous vitreomacular traction and/or macular hole resolution, resolution of vitreomacular traction and/or macular hole through vitrectomy, failure of vitrectomy to resolve macular hole, spontaneous development of a macular hole, or death (see 3.16 and 3.19 for model transitions). There were 2 assumptions in the model that were based only on the manufacturer's clinical expert opinion:

- There is a maximum of 2 vitrectomies. This is based on clinical expert opinion that the probability of having a third vitrectomy was very low.
- Vitrectomies are 100% effective at treating vitreomacular traction, and therefore a second one is only used to close a persistent macular hole.

3.15 Within each health state of the long-term extrapolation Markov model (other than death) there were 6 sub-states that represented levels of visual acuity, called the vision health states. Patients could move in any direction through the vision health states because they could improve or deteriorate. These health states were determined by the patients' BCVA in terms of ETDRS letters read: VA1: 76–100 letters, VA2: 66–75 letters, VA3: 56–65 letters, VA4: 46–55 letters, VA5: 36–45 letters, VA6: 0–35 letters.

Model transitions

- 3.16 The transitions between health states in the manufacturer's decision tree and Markov models were calculated from the integrated phase III trial data (from TG-MV-006/007), with the following exceptions: probability of opting for a second vitrectomy (75%), probability of success of second vitrectomy (50% of success rate of first vitrectomy [probability of macular hole closure post-vitrectomy was estimated as 82%]). Each of these were based on manufacturer expert opinion.
- 3.17 The mortality rates applied in the manufacturer's model were based on VA state. For VA1–5, the mortality rate of the general population was used, taken from England and Wales interim life tables 2008–2010, from the Office of National Statistics. These were weighted according to sex. For a best-seeing eye VA6 score, which represented severe visual impairment, the manufacturer used a mortality hazard rate of 1.54 from a US study (Christ et al. 2008).
- 3.18 As described in 3.15, the manufacturer's Markov model included visual acuity states within each health state. At the start of the model, the distribution of patients across the visual acuity states was estimated using an ordered logit model based on trial data (TG-MV-006 and TG-MV-007). This was assumed to be the same for both treatment arms (ocriclasmin and placebo). The presence of a macular hole affected the visual acuity state distribution, with more patients with a macular hole having VA3–VA6 scores than those without.
- 3.19 Patients could move between any visual acuity state (representing improving or declining visual acuity) within the model. The transition probabilities between visual acuity states were assumed to be different depending on whether vitreomacular adhesion/traction was resolved or remained unresolved, and it was assumed that the presence of a macular hole did not affect the rate of visual acuity change. The transition probabilities between visual acuity states were based on estimates from the literature that relate to changes over time in the general population for patients with resolved vitreomacular traction, and in patients with persistent vitreomacular traction for unresolved vitreomacular traction. The manufacturer's submission recognised that after specific events there would be an initial change in vision that would be different from changes observed in the general population over time. The manufacturer therefore

included within the model visual acuity transitions after a specific event for 1 cycle. The events that were modelled were vitreomacular traction resolution only, macular hole closure only, vitreomacular traction resolution and macular hole closure and vitreomacular traction progression to macular hole. The corresponding transition probabilities were calculated from the integrated phase III clinical trial data (TG-MV-006 and TG-MV-007) using an ordered logit model (except for the macular hole opening, for which calibration was used).

Utility values and adverse events

- 3.20 The manufacturer applied utility values to each of the visual acuity states in the model. These were derived from a study that used contact lenses to simulate the effects of visual impairment caused by age-related macular degeneration. The study grouped patients into 4 categories, according to their best-seeing eye, and a time trade-off instrument was used to elicit utilities from the general UK population. Because the manufacturer's model used 6 visual acuity states, the utility values from the study were adapted to fit the 6 visual acuity states in the model. In addition, because the study was based on the best-seeing eye only, a matrix was developed to account for the visual acuity state of both the best- and worst-seeing eye. The utility for each visual acuity combination (for example, VA1 and VA1, or VA1 and VA2) was then estimated.
- 3.21 The adverse events included in the manufacturer's model were modelled as occurring post-vitreotomy or post-ocriclasmin. These included retinal tear (13.23% and 0.22%, respectively), retinal detachment (13.23% and 0.43% respectively), elevated intraocular pressure (26.46% and 2.37% respectively) and vitreous haemorrhage (3.31% and 0.22% respectively). The probabilities of these events occurring were estimated using the integrated clinical trials data (TG-MV-006 and TG-MV-007).
- 3.22 Many patients develop cataracts after vitrectomy, therefore the manufacturer's model included a 96% probability (determined from published data) of developing cataracts after having a vitrectomy. The proportions of people in each subgroup who could develop cataracts (who have not had previous cataract surgery) were 59% for VMT with ERM, 63.9% for VMT without ERM and 79.1% for VMT with MH.

3.23 The manufacturer accounted for adverse events by applying disutility values. A disutility for metamorphopsia (0.017), which has a significant impact on quality of life, was derived from the literature and included in the manufacturer's model. Disutility values derived from the literature were also applied to each of the adverse events captured in the model (see 3.21): retinal detachment (0.13 for 1 month), vitreous haemorrhage (0.02 for 1 month) and cataract (0.14 for 6 months). Disutility values for retinal tear and increased intraocular pressure were not identified in the literature and therefore no disutility was applied to these. Disutilities were all applied during 1 cycle, with an exception made for metamorphopsia, which persisted until vitreomacular traction resolved. Disutilities were normalised to a 3-month cycle length. Vitrectomy surgery is associated with a post-surgery reduction in health-related quality of life which was accounted for in the model by transitioning to the visual acuity state VA6 for 2 weeks (rather than applying a disutility value).

Costs applied in the model

3.24 The manufacturer's model included the following costs: ocriplasmin (£2500), ocriplasmin administration (£117), surgery (vitrectomy [£2191] and cataract [£851]), follow-up visits (£80), OCT (£54.29), annual cost of blindness (£6496), and costs of adverse events (retinal detachment [£2012], retinal tears [£424], increased intraocular pressure [£40.65], vitreous haemorrhage [£1852]). The manufacturer used NHS reference costs to estimate the cost of vitrectomy surgery, cataract surgery, administration of ocriplasmin, follow-up visits, retinal detachment, and vitreous haemorrhage. The annual cost of blindness was estimated from the Personal Social Services Research Unit (PSSRU) costs of Health and Social Care and accounts for residential care (£18,191 for 30% of blind patients), community care (£8195 for 6% of blind patients), depression (£539 for 39% of blind patients), and hip replacement (£6728 for 5% of blind patients). The cost of OCT was taken from the literature, and the costs of retinal tears and increased ocular pressure were taken from NICE submissions. The model base case assumes 1 follow-up visit per 3 months, 1 OCT per 3 months, 4 post-vitrectomy follow-up visits, 4 OCTs post-vitrectomy, 2 follow-up visits post-ocriplasmin injection and 1 OCT post-ocriplasmin injection. These visit estimates are based on clinical expert advice.

Manufacturer's base-case incremental cost-effectiveness ratio (ICER), sensitivity and scenario analyses

- 3.25 The manufacturer presented a base-case ICER for each patient subgroup. The ICER for ocriplasmin compared with 'watch and wait' in the VMT without ERM subgroup was £18,481 per quality-adjusted life year (QALY) gained (incremental cost: £1880.67, incremental QALY: 0.1018), for VMT with ERM it was £67,119 per QALY gained (incremental cost: £2487.13, incremental QALY: 0.0371) and for VMT with MH it was £21,593 per QALY gained (incremental cost: £1752.90, incremental QALY: 0.0812). The manufacturer estimated that the probability of ocriplasmin being cost effective, if the maximum acceptable ICER was £20,000 or £30,000 per QALY gained, compared with 'watch and wait' was: 51% and 80% respectively for VMT without ERM; 0% and 2% respectively for VMT with ERM; and 46% and 72% respectively for VMT with MH.
- 3.26 The manufacturer conducted univariate sensitivity analyses for each of the subgroups. For the VMT without ERM and VMT with ERM subgroups the model outcomes were most sensitive to the inputs determining non-surgical resolution of vitreomacular traction at 6 months and 28 days. The QALY discount rate was also an important driver for these subgroups. For the VMT with MH subgroup, the model outcomes were most sensitive to the inputs that determined non-surgical macular hole closure, cataract disutility and the chance of macular hole closure post-vitrectomy.
- 3.27 The manufacturer also conducted scenario analyses to investigate the following:
- The time limit of vitrectomy. It was assumed that vitrectomies would occur within 2 years in the base case and therefore the model applied a 3-month cycle length for 2 years and an annual cycle length thereafter. The 3-month cycles enable rapid changes in visual acuity in response to vitrectomy. By changing the length of time the model was running at 3-monthly cycles from 2 years in the base case to 1 or 5 years, the manufacturer could investigate the impact of changing the time period for vitrectomy.

- The impact of treating patients with a macular hole earlier than usual with a vitrectomy by assessing the cost effectiveness at day 28 of ocriclasmin compared with vitrectomy.
- Accounting for the lack of mortality in the decision tree part of the model by doubling mortality in the first year of the Markov model.
- Using visual acuity state transitions derived from a study by Van der Pols et al. (2000) on British patients, rather than Finnish patients as in the base case.
- Applying the same rate of visual acuity decline whether vitreomacular traction was resolved or not, by using the transition rates from Laitinen et al. (2005) for all visual acuity health states.
- Using spontaneous vitreomacular traction resolution rates from the literature rather than the clinical trial.
- Applying utility values derived from patients with age-related macular degeneration in the US, rather than utilities derived from the general UK population as in the base case.
- The impact of modelling the best or worst-seeing eye only, rather than accounting for both eyes.
- Applying an alternative metamorphopsia disutility value of 0.14, derived using the EQ-5D, rather than 0.017 from the literature as used in the base case.

3.28 The different scenarios had different impacts on the 3 subgroups. Two scenarios increased the ICER the most. These increased the ICER substantially from the manufacturer's base case for the VMT without ERM and VMT with ERM subgroups and resulted in small increases for the VMT with MH group:

- making the long-term vision transition rates equal whether vitreomacular traction had resolved or not
 - VMT without ERM: £44,489 per QALY gained (incremental cost £2235, incremental QALY 0.050)

- VMT with ERM: £142,347 per QALY gained (incremental cost £2599, incremental QALY 0.018)
- VMT with MH: £21,723 per QALY gained (incremental cost £1754, incremental QALY 0.081)
- using a 16.5% rate of spontaneous resolution
 - VMT without ERM: £67,320 per QALY gained (incremental cost £2257, incremental QALY 0.034)
 - VMT with ERM: £230,656 per QALY gained (incremental cost £2575, incremental QALY 0.011)
 - VMT with MH: £21,615 per QALY gained (incremental cost £1753, incremental QALY 0.081).

3.29 Applying a different metamorphopsia disutility value reduced the ICER substantially from the manufacturer's base case in all 3 subgroups:

- VMT without ERM: £12,190 per QALY gained (incremental cost £1881, incremental QALY 0.154)
- VMT with ERM £42,388 per QALY gained (incremental cost £2487, incremental QALY 0.059)
- VMT with MH £17,837 per QALY gained (incremental cost £1753, incremental QALY 0.098).

3.30 Modelling only the best-seeing eye reduced the ICER and modelling only the worst-seeing eye increased the ICER in all 3 subgroups, with a large impact for both analyses in the VMT with ERM subgroup. Using utility values derived from UK patients increased the ICER for all 3 subgroups, with a substantial increase in the VMT with ERM subgroup. Changing the time limit of vitrectomy had little impact on the VMT with MH subgroup but for both the VMT without ERM and VMT with ERM subgroups using 1 year substantially decreased the ICER, and using 5 years substantially increased the ICER. The other scenario analyses had only a small impact on the ICERs.

Evidence Review Group comments

Clinical effectiveness

- 3.31 The ERG reviewed the manufacturer's literature review and considered that the manufacturer was likely to have identified all the randomised controlled trial evidence relevant to the decision problem. The ERG reviewed the designs of TG-MV-006 and TG-MV-007. It noted that the patients in the placebo group had undergone an injection, which was an invasive procedure, rather than having been initially observed without treatment, as is typical in UK clinical practice.
- 3.32 The ERG noted that the visual acuity of patients enrolled on the trials, with the exception of those with a macular hole, was better than would be seen in clinical practice for patients with vitreomacular traction and/or macular hole who would normally be offered vitrectomy. The ERG identified this as a limitation of the data because efficacy may be affected by disease severity.
- 3.33 The ERG noted that the primary outcome of non-surgical resolution of vitreomacular adhesion is a surrogate outcome for preventing deteriorating vision, which can result from untreated and progressive vitreomacular traction. The ERG commented that there is limited evidence on the validity of non-surgical resolution of vitreomacular adhesion as a surrogate for preventing deteriorating visual function.
- 3.34 The ERG noted that adverse events reported in the pooled results of 7 completed clinical trials (the 'safety set') were consistent with the vitreolytic activity of the drug or method of administration and most were mild, or moderate and transient. However, the ERG commented that none of the safety set of trials, which ocriplasmin's safety profile is based on, was designed to assess safety outcomes with sufficient power to detect differences in incidence rates. This safety set can only detect adverse events with an incidence greater than 0.4% because of the uneven randomisation ratios.

Cost effectiveness

3.35 The ERG considered the modelling approach presented by the manufacturer to be appropriate and stated that it enabled important anatomical and visual outcomes to be simultaneously captured in the short and long term. The ERG reviewed the model, and considered many of the approaches, assumptions and data sources applied by the manufacturer to be reasonable.

3.36 The ERG identified some areas of uncertainty in the manufacturer's model, which it investigated, if it was possible, in exploratory analyses. Three scenarios had a large impact on the ICER:

- applying a different rate of probability for cataracts (see 3.38)
- enabling cataract and vitrectomy surgery to be done simultaneously (see 3.39)
- applying a different macular hole vitrectomy success rate (see 3.40).

Evidence Review Group's exploratory analyses

3.37 Most of the ERG's exploratory analyses did not affect the manufacturer's base-case ICERs (see [3.25](#)) for the subgroups substantially. The resulting ICERs were in the following ranges:

- VMT without ERM:
 - base case: £18,481 per QALY gained
 - range: £17,733–£18,986 per QALY gained
- VMT with ERM:
 - base case: £67,119 per QALY gained
 - range: £64,331–£67,666 per QALY gained
- VMT with MH:
 - base case: £21,593 per QALY gained
 - range: £20,551–£22,985 per QALY gained.

- 3.38 The ERG explored the rate of cataracts after vitrectomy. The ERG noted that a study of the National Ophthalmology Database identified that 64.6% of eyes that had a macular hole operation (without combined or previous cataract surgery) needed lens removal within 1 year of vitrectomy, which was much lower than the 96% applied in the model by the manufacturer (to non-pseudophakic eyes only). Applying this new rate increased the ICER of each subgroup by at least £1000 (VMT without ERM: from £18,481 to £19,858 per QALY gained [incremental cost £1899, incremental QALY 0.096]; VMT with ERM: £67,119 to £71,737 per QALY gained [incremental cost £2494, incremental QALY 0.035]; VMT with MH: from £21,593 to £28,289 per QALY gained [incremental cost £1806, incremental QALY 0.064]). The ERG conducted a sensitivity analysis around this and applied an 88.8% and 92.0% probability of cataract. This increased the manufacturer's base-case ICER, but to a lesser extent than applying the 64.6% probability. Applying an 88.8% probability of cataract increased the manufacturer's base-case ICER to: VMT without ERM: £18,782 per QALY gained (incremental cost £1885, incremental QALY 0.100); VMT with ERM: £68,127 per QALY gained (incremental cost £2489, incremental QALY 0.037); VMT with MH: £22,863 per QALY gained (incremental cost £1765, incremental QALY 0.077). Applying a 92.0% probability of cataract increased the manufacturer's base-case ICER to: VMT without ERM: £18,647 per QALY gained (incremental cost £1883, incremental QALY 0.101); VMT with ERM: £67,675 per QALY gained (incremental cost £2488, incremental QALY 0.037); VMT with MH: £22,283 per QALY gained (incremental cost £1760, incremental QALY 0.079).
- 3.39 The ERG explored the impact of combining vitrectomy and cataract surgery. The ERG received advice from clinical specialists highlighting that, as a result of the high incidence of cataract formation after vitrectomy, lens removal is frequently combined with vitrectomy as a preventative measure. The ERG noted that this was not accounted for in the manufacturer's model. Furthermore, the ERG noted that Jackson et al. (2013) report that 40.5% of patients undergoing macular hole vitrectomy had combined lens removal. Therefore, to investigate the potential impact of combined surgery on the manufacturer's ICERs, the ERG further reduced the probability of cataract surgery by 40.5%. The ICER of each subgroup increased (VMT without ERM: from £18,481 to £20,212 per QALY gained [incremental cost £1904,

incremental QALY 0.094]; VMT with ERM: £67,119 to £72,929 per QALY gained [incremental cost £2496, incremental QALY 0.034]; VMT with MH: from £21,593 to £30,458 per QALY gained [incremental cost £1818, incremental QALY 0.060]).

3.40 The ERG explored the success rate of macular hole vitrectomy in the manufacturer's model. The ERG noted that 82% of vitrectomies to treat macular hole are assumed to be successful (based on trial data) in the manufacturer's base-case economic analyses. However, expert clinical opinion highlighted that, in patients with a macular hole of 400 micrometres or less, success after vitrectomy involving internal limiting membrane peeling is over 90%. Therefore the ERG carried out a sensitivity analysis assuming 95.8% of macular hole vitrectomies are successful. The ICER associated with each subgroup increased, most notably in patients with a macular hole (VMT without ERM: from £18,481 to £19,250 per QALY gained [incremental cost £1911, incremental QALY 0.099]; VMT with ERM: from £67,119 to £69,588 per QALY gained [incremental cost £2501, incremental QALY 0.036]; VMT with MH: from £21,593 to £26,854 per QALY gained [incremental cost £1847, incremental QALY 0.069]).

3.41 The ERG estimated a revised (deterministic) base-case ICER for each subgroup that took into account all of the exploratory analyses detailed in 3.37–3.40, and used a probability of cataract of 64.6%. The resulting ICERs were:

- VMT without ERM £20,861 per QALY gained (incremental costs £2082, incremental QALY 0.100)
- VMT with ERM £69,694 per QALY gained (incremental costs £2568, incremental QALY 0.037)
- VMT with MH £56,137 per QALY gained (incremental costs £2132, incremental QALY 0.038).

3.42 The ERG commented that there were other areas of uncertainty that could affect the ICER, including:

- The uncertainty associated with the clinical data because patients receiving a placebo injection had been used to represent the outcomes of 'watch and wait' patients. The ERG concluded that this was likely to bias against ocriplasmin, and that the ICER would be expected to decrease (in all subgroups) if this was addressed.
- The health states modelled did not include epiretinal membrane. The ERG stated that this would affect only the VMT with ERM subgroup but would be likely to increase the ICER in this subgroup.
- Differences in the results and baseline characteristics within and between the relevant clinical trials (TG-MV-006 and TG-MV-007). The ERG concluded that any bias was likely to be against ocriplasmin and therefore the ICER would be expected to decrease if baseline characteristics for these subgroups were balanced.
- The manufacturer conservatively assuming long-term vision decline was the same for all patients with unresolved vitreomacular traction, regardless of whether they had a macular hole or not. The ERG stated that the ICER would be expected to decrease if visual decline was different for vitreomacular traction patients with or without a macular hole but that the impact was not quantifiable for any of the subgroups.
- The manufacturer assuming the quality of life impact of metamorphopsia is the same for both vitreomacular traction and macular hole, and applies to patients whose vitreomacular traction is unresolved, or whose macular hole is open. The ERG considered these assumptions to be potentially inaccurate because the patient population in Fukeda et al. (2009) continued to have symptoms of metamorphopsia after vitrectomy to close the macular hole. This suggests the possibility of metamorphopsia in patients with resolved vitreomacular traction, which clinical specialist advice highlighted may be a result of a persistent epiretinal membrane (not accounted for in the manufacturer's model). The ERG concluded that the impact of accounting for metamorphopsia in patients with resolved vitreomacular traction was not quantifiable but that any bias was likely to be small and against ocriplasmin. The ICER would be expected to decrease if a lower disutility for metamorphopsia was applied in patients with vitreomacular traction alone (no macular hole).

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- The fact that the manufacturer provided no rationale for not including an increased mortality risk in patients with 'some' visual impairment. The ERG anticipated that the impact on the ICER of incorporating an increased mortality risk for patients with visual impairment in their worst-seeing eye was likely to be small, and that the direction of any bias was unclear.

3.43 The ERG reviewed the scenario presented by the manufacturer in which long-term vision outcomes were assumed to be equivalent, whether vitreomacular traction was resolved or unresolved. It noted that this increased the ICER substantially (see 3.28). The ERG agreed with the manufacturer and stated that, based on the ERG's clinical specialist opinion, this scenario was unlikely.

3.44 Full details of all the evidence are in the [manufacturer's submission](#) and the [ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ocriplasmin having considered evidence on the nature of vitreomacular traction and the value placed on the benefits of ocriplasmin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee considered the current management of vitreomacular traction and the likely place of ocriplasmin in clinical practice; noting that the scope of the appraisal and the marketing authorisation for ocriplasmin is 'indicated in adults for the treatment of vitreomacular traction, including when associated with macular hole of diameter less than or equal to 400 microns'. The clinical specialists explained that vitreomacular traction was managed differently depending on whether or not a stage II macular hole was present.
- They said that patients who presented with a stage II macular hole would be listed for surgery because delaying surgery could lead to poorer outcomes for these patients and stage II macular holes rarely resolve spontaneously. The Committee heard from the clinical specialists that if ocriplasmin was recommended for use, patients with a stage II macular hole would still be listed for surgery, without delay, and ocriplasmin would be administered to patients during the period before surgery (in UK clinical practice this can be a number of weeks or months).
 - The clinical specialists stated that for patients who have vitreomacular traction without a macular hole, or with a stage I macular hole, delaying surgery in general does not have an impact on long-term outcomes and that many of these patients will not need surgery. The clinical specialists explained that some patients would need surgery and in these patients if ocriplasmin was available it would be offered as an alternative to surgery. Furthermore, they commented that some patients would have severe distressing symptoms (such as metamorphopsia [distorted vision in which straight lines appear wavy] and low visual acuity), but would not be eligible for surgery, and that if ocriplasmin was available it would be offered to these patients instead of 'watch and wait'. The Committee acknowledged that about 80% of the patients in the trials had an expected need for vitrectomy at baseline, and therefore the patients in the trials were those with severe distressing symptoms and/or those who were eligible for surgery.

- The Committee concluded that the treatment pathway varies depending on the presence or absence of a stage II macular hole. If a stage II macular hole is present, ocriplasmin would be used during the wait for surgery, without delaying surgery. If a stage II macular hole is not present, ocriplasmin would be used as an alternative to surgery, or as an alternative to 'watch and wait' for people who have severe distressing symptoms.

- 4.3 The Committee discussed vitrectomy surgery in UK clinical practice. The clinical specialists explained that there were risks involved with the surgery, including the potential to damage the eye and reduce visual acuity. Clinical specialists stated that a treatment that could avoid vitrectomy surgery would be beneficial for patients. The Committee also heard from the patient expert who described her experience of vitrectomy surgery and the anxiety and trauma it could cause. The patient expert explained that the recovery period after surgery was worse than the surgery itself because she had to lie in a face down position for up to a week. She described this as being very difficult and uncomfortable, and said that it felt suffocating. She commented that she would choose a treatment that involved an injection over vitrectomy surgery. The Committee recognised this, but also understood that face down positioning for recovery is being used less often, and for shorter periods. The Committee acknowledged that, although vitrectomy surgery was effective in resolving vitreomacular traction and the recovery time after surgery was short, the recovery was an unpleasant process for patients, and surgery also had risks and could damage the eye. The Committee concluded that an alternative treatment for vitreomacular traction would be welcomed by clinicians and patients.
- 4.4 The Committee considered the impact of vitreomacular traction on the everyday life of patients. It heard from the patient expert about the problems associated with vitreomacular traction, including difficulties with reading, cooking, watching television and driving that prevented them from enjoying these activities. The Committee understood from the patient expert that the effects of metamorphopsia and macular holes were very disturbing. The patient described seeing straight lines as wavy, and objects disappearing from view. The Committee concluded that resolving vitreomacular traction without the need for surgery would be beneficial to the wellbeing of patients with vitreomacular traction.

Clinical effectiveness

- 4.5 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of ocriplasmin. The Committee acknowledged that 3 subgroups were presented by the manufacturer (VMT without ERM [vitreomacular traction without an epiretinal membrane], VMT with ERM [vitreomacular traction with an epiretinal membrane], and VMT with MH [vitreomacular traction with a stage II macular hole]). It noted that the evidence was from the TG-MV-006 and TG-MV-007 trials and it discussed the outcomes in these trials. The Committee acknowledged that the outcomes presented by the manufacturer were in line with the scope issued by NICE, and that they included vitreomacular traction resolution, posterior vitreous detachment (PVD), vitrectomy, visual acuity changes and macular hole closure. The Committee noted that although there was a statistically significant benefit with ocriplasmin compared with placebo in terms of vitreomacular traction resolution and total PVD at day 28 in the VMT without ERM and VMT with MH subgroups, this did not translate into a statistically significant visual acuity benefit (see 3.7 and 3.9). The clinical specialists explained that visual acuity was not a complete or accurate measure of the vision impairment experienced with vitreomacular traction. This is because measured visual acuity may not be affected by the presence of a macular hole or metamorphopsia: although the patient has distorted vision, they may still be able to read a letter on an eye chart successfully. The clinical specialists therefore explained that anatomical measures such as vitreomacular traction resolution or total PVD were a better way to measure the benefit of the treatment, and that from their experience approximately 70–80% of metamorphopsia resolved with vitreomacular traction resolution. The Committee accepted that the anatomical outcomes of vitreomacular traction resolution and total PVD were appropriate measures for assessing the effectiveness of ocriplasmin.
- 4.6 The Committee considered the results from the trials in the manufacturer's submission. The Committee noted that the efficacy of ocriplasmin was not the same for all the subgroups evaluated. The Committee acknowledged that ocriplasmin was associated with a statistically significant improvement in vitreomacular traction resolution and total PVD at 28 days in the VMT without ERM (see 3.7) and VMT with MH (see 3.9) subgroups. However, in the VMT

with ERM subgroup, the effect of ocriplasmin in terms of these outcomes was small and not statistically significant (see 3.8). The Committee heard from the clinical specialists that they did not consider ocriplasmin to have a place in the treatment of patients with vitreomacular traction and an epiretinal membrane because it was not clinically effective in these patients. The Committee recognised that the VMT with MH group included people with ERM, and that because of the small sample size of this group (n=23) analyses had not been presented by the manufacturer. The Committee took into account the data from the VMT with ERM subgroup and the opinion of the clinical specialists and concluded that ocriplasmin was unlikely to be clinically effective in people with ERM in any of the subgroups, including VMT with MH. The Committee concluded that ocriplasmin was clinically effective, in terms of vitreomacular traction resolution and total PVD at 28 days in the subgroups VMT without ERM and VMT with MH, but not in the subgroup VMT with ERM, and it was unlikely to be clinically effective in terms of these outcomes in the VMT with MH subgroup who had ERM.

- 4.7 The Committee discussed whether the comparator arm in the clinical trials was relevant to clinical practice in the UK. It noted that a placebo injection was used in the trials instead of the UK clinical practice of 'watch and wait'. It heard from clinical specialists that an injection of saline into the eye sometimes resolves vitreomacular traction, and that it could also provoke macular hole development. Therefore it was likely that the placebo injection could lead to total PVD, or to the creation of a macular hole. The clinical specialists commented that this was supported by the spontaneous resolution rates observed in the placebo arm of the trials (approximately 10%) because they were much higher than they observe in clinical practice (approximately 2–5%). The Committee concluded that the placebo injection in the clinical trials was not equivalent to 'watch and wait' and that it was plausible that the efficacy of ocriplasmin would have been greater if it had been compared with the UK clinical practice of 'watch and wait'.
- 4.8 The Committee considered the differences between the trials and clinical practice in the UK. The clinical specialists noted that access to surgery may have been quicker in the trials than in clinical practice. It discussed that patients in the trials may be operated on immediately, while in clinical practice

there could be a waiting time of several weeks or months. The Committee agreed that this difference could lead to an underestimation of the benefit of ocriplasmin because the wait for surgery can result in a poorer outcome for patients in clinical practice than observed in the trial. The Committee concluded that the benefit of ocriplasmin may have been underestimated because there was a shorter waiting period for vitrectomy in the clinical trials.

- 4.9 The Committee considered the impact of ocriplasmin on all of the outcomes measured in the trials. The Committee noted that the trial results were limited to 6 months after the injection and therefore the long-term impact was unknown. However, it heard from clinical specialists that once traction was relieved the condition was generally stable, and therefore it was plausible that any benefits relating to ocriplasmin would be expected to last beyond the 6-month clinical trial period. The Committee concluded that the clinical effectiveness of ocriplasmin was likely to be durable in the long term.
- 4.10 The Committee considered the adverse events that were associated with ocriplasmin. It noted that adverse events were mainly ocular events and that the incidence of serious adverse events was similar between ocriplasmin and placebo. The Committee acknowledged that the most common serious adverse event reported in the study eye was macular hole, which was more common in the placebo group than in the ocriplasmin group. The Committee understood that most adverse events were non-serious, mild in intensity and generally resolved. It concluded that ocriplasmin was similar to placebo in terms of adverse events.

Cost effectiveness

- 4.11 The Committee considered the cost-effectiveness evidence presented in the manufacturer's submission, including the base-case incremental cost-effectiveness ratios (ICERs), the sensitivity and scenario analyses, the Evidence Review Group's (ERG's) critique of the manufacturer's evidence, and comments raised during consultation on the appraisal consultation document (ACD). The Committee considered the 3 subgroups presented by the manufacturer in turn, as detailed below.

- 4.12 The Committee considered the available cost-effectiveness evidence for ocriplasmin in the VMT without ERM subgroup. The Committee discussed the potential for ocriplasmin to be used earlier than surgery would normally be used, in patients with distressing symptoms (for example metamorphopsia or low visual acuity), and was satisfied that this was captured in the model. It discussed the manufacturer's base-case ICER of £18,500 per quality-adjusted life year (QALY) gained. It noted that in the ERG's exploratory analysis (see [3.37–3.41](#)) the ICERs were in the range of £17,700 to £20,200 per QALY gained, and that the ERG base-case ICER was £20,900 per QALY gained. The Committee recognised that this subgroup represents people with vitreomacular traction without an epiretinal membrane or a stage II macular hole who would be eligible for vitrectomy surgery, or people with severe distressing symptoms who would not be eligible for surgery. The Committee concluded that ocriplasmin was a cost-effective option for the treatment of people with vitreomacular traction without an epiretinal membrane, and without a stage II macular hole.
- 4.13 The Committee considered the available cost-effectiveness evidence of ocriplasmin in the VMT with ERM subgroup. The Committee noted that ocriplasmin was not associated with a statistically significant improvement in vitreomacular traction resolution and total PVD at 28 days in the VMT with ERM subgroup (see [3.8](#)), and that any differences observed between ocriplasmin and placebo were small. Taking into account these data and the view of the clinical specialists that ocriplasmin was not effective in patients with ERM, the Committee concluded that the use of ocriplasmin in people with vitreomacular traction with an epiretinal membrane, but without a stage II macular hole, was not a cost-effective use of NHS resources.
- 4.14 The Committee considered the cost effectiveness of ocriplasmin in the VMT with MH subgroup. It noted the manufacturer's base-case ICER of £21,600 per QALY gained. It discussed the manufacturer's sensitivity and scenario analysis (see [3.25–3.30](#)), and the ERG critique of the manufacturer's model. It noted the uncertainties in the model, which had potentially substantial impacts on the manufacturer's ICER:
- The impact of combining vitrectomy and cataract surgery (see [4.15](#)).

- The rate of cataracts (see 4.16).
- The macular hole vitrectomy success rate (see 4.17).
- The metamorphopsia utility value (see 4.18).

The Committee also discussed additional comments that were raised during ACD consultation (see 4.19) and that could impact on the ICER, including:

- The number of optical coherence tomography (OCT) and follow-up visits post-vitrectomy.
- The retinal detachment rate.
- The retinal tear rate.
- The rate of visual decline not accounting for a macular hole.

The Committee's discussion and conclusion are summarised in the paragraphs below.

- 4.15 The Committee considered the VMT and MH subgroup and the assumption in the manufacturer's model that vitrectomy and cataract surgery would not be performed at the same time. The Committee heard from clinical specialists that combining vitrectomy surgery and cataract surgery into one procedure is common practice in the UK. It noted that the risk of cataracts forming after vitrectomy surgery is greater than 90%. However, the clinical specialists explained that the main driver for performing the 2 operations at the same time was constrained capacity in hospital eye departments rather than improved outcomes. The Committee agreed that combining vitrectomy and cataract surgery was done in clinical practice, and therefore should be included in the model. It noted that combining vitrectomy and cataract surgery increased the ICER for the VMT with MH subgroup from £21,600 to approximately £30,500 per QALY gained. The Committee noted that no disutility had been applied by the manufacturer to the model to account for the addition of cataract removal to vitrectomy surgery, and concluded that applying a disutility would reduce the ICER marginally to under £30,500 per QALY gained.

- 4.16 The Committee discussed the VMT and MH subgroup further, and the rate that was applied in the manufacturer's model for developing a cataract after vitrectomy. The Committee noted from the ERG's critique that as the rate of developing a post-surgical cataract is reduced, the ICER for ocriplasmin increases. The Committee heard from clinical specialists that the overall chance of developing a cataract was likely to be greater than 90%. It commented further that the annual rate of 64.6% (estimating an ICER of £28,300 per QALY gained for the VMT and MH subgroup) modelled by the ERG was likely to be lower than observed in UK clinical practice, and that the rate modelled by the manufacturer (96% annual rate, ICER £21,600 per QALY gained for the VMT with MH subgroup) was likely to be higher than observed in UK clinical practice. The Committee concluded that the rate of developing a cataract in UK clinical practice was likely to be lower than the manufacturer's value.
- 4.17 The Committee discussed the success rates of macular hole vitrectomy applied to the VMT with MH subgroup in the manufacturer's model (82%) and applied in the ERG's exploratory analyses (95.8%). It noted that for the VMT with MH subgroup, applying the higher rate increased the ICER from £21,600 to £26,900 per QALY gained. The Committee heard from clinical specialists that the success rate generally ranged from 80 to 90% and acknowledged the comments raised during ACD consultation that supported the ERG's macular hole vitrectomy success rate. The Committee therefore considered the rate applied by the ERG to be the most appropriate. The Committee concluded that the macular hole vitrectomy success rate was likely to be higher than that modelled in the manufacturer's base case and that this would increase the ICER.
- 4.18 The Committee noted from the manufacturer's scenario analysis in the VMT with MH subgroup that changing the metamorphopsia utility value had an impact on the manufacturer's base-case ICER. It understood that the manufacturer's base case applied a disutility value of 0.017 and that the manufacturer's scenario analysis, using a value of 0.14, reduced the ICER in all 3 subgroups substantially (see 3.29). The Committee heard from clinical specialists that the utility gained from resolving metamorphopsia could be equivalent to going up 2 visual acuity states. The Committee considered that

this was equivalent to approximately 0.03 utilities, based on the utility values used in the manufacturer's model. The Committee concluded that the disutility value applied in the manufacturer's model underestimated the disutility of metamorphopsia and that applying a higher disutility value would reduce the ICER, although the level of impact remained unclear.

- 4.19 The Committee considered the comments that were received during ACD consultation. It noted that the number of OCT and follow-up visits post-vitreotomy may have been overestimated in the manufacturer's base case for the VMT with MH subgroup. The Committee was aware that the ERG had done a sensitivity analysis that reduced the number of OCT and follow-up visits from 4 to 2, and that this increased the ICER by a small amount: from £21,600 to £22,500 per QALY gained. The Committee also discussed comments received during consultation that a retinal detachment rate of 13.23% in the manufacturer's base case seemed high and a rate of 5.4% was more representative of clinical practice. In addition, a retinal tear rate with ocriplasmin of 0.22% had been used in the manufacturer's base case rather than a rate of 1.3%, which has been published. The Committee considered the impact on the ICER of the different rates of retinal detachment and retinal tear and recognised that the ICER would increase by a small amount. Finally, the Committee also noted comments received during consultation that in the manufacturer's base case visual decline was assumed to be the same whether or not a macular hole was present. The Committee understood from the ERG that the ICER would reduce if visual decline was different for people with or without a macular hole. The Committee concluded that reducing the number of OCT and follow-up visits and applying different rates for retinal detachment and retinal tear would lead to small increases in the ICER, but that accounting for a greater rate of visual decline with a macular hole would reduce the ICER.
- 4.20 The Committee considered whether an ocriplasmin injection is an innovative treatment. The Committee agreed with the clinical specialists and manufacturer that the ocriplasmin injection provided a step change in treating patients with vitreomacular traction compared with current practice in vitrectomy and 'watch and wait'. The Committee acknowledged that no significant or substantial health-related benefits were identified that were not included in the economic model. Therefore the Committee agreed that the

ocriplasmin injection was innovative and it would consider an ICER at the top end of the range that would normally be considered a cost effective use of NHS resources (£20,000–30,000 per QALY gained).

4.21 In summary, the Committee considered the manufacturer's base-case ICERs, the sensitivity and scenario analyses presented by the manufacturer, the ERG's critique and exploratory analyses, and comments raised during consultation for each of the subgroups presented that make up the marketing authorisation.

- The Committee considered the use of ocriplasmin to treat vitreomacular traction without an epiretinal membrane or a stage II macular hole and concluded that the ICER was likely to be no greater than £20,900 per QALY gained (as presented by the ERG, see 3.41). It agreed therefore that ocriplasmin was a cost-effective use of NHS resources for treating vitreomacular traction in people with vitreomacular traction without an epiretinal membrane.
- The Committee considered the use of ocriplasmin to treat vitreomacular traction with an epiretinal membrane, but without a stage II macular hole, and recognised that ocriplasmin was not clinically effective or cost effective for these people (see 3.8 and 3.41). The Committee therefore concluded that ocriplasmin could not be considered a cost-effective use of NHS resources for treating people with vitreomacular traction and an epiretinal membrane, without a stage II macular hole.
- The Committee considered the use of ocriplasmin to treat vitreomacular traction with a stage II macular hole. The Committee agreed that the preferred assumption was to include combined cataract and vitrectomy surgery (see 4.15), and noted the associated ICER was approximately £30,500 per QALY gained. It considered that in clinical practice the effectiveness of ocriplasmin might be greater than that seen in the trials because patients would have to wait longer for surgery and would not benefit from a placebo injection (see 4.7). The Committee recognised that this would lower the ICER to below £30,500 per QALY gained. The Committee also considered that addressing uncertainties in the model could both increase and decrease the ICER (increase it by: increasing the macular hole vitrectomy success rate [see 4.17], reducing the post vitrectomy cataract rate [see 4.16], increasing the retinal tear rate with ocriplasmin [see 4.19], decreasing the retinal detachment rate with vitrectomy [see 4.19] and decreasing the post-vitrectomy OCT and follow-up

visits [see 4.19]; decrease it by: accounting for greater disutility values associated with both metamorphopsia and combined surgery [see 4.15 and 4.18], accounting for a greater rate of visual decline with a macular hole [see 4.19], and accounting for the active placebo comparison [see 4.7]). The Committee recognised that ocriplasmin was unlikely to be clinically effective in patients who have an epiretinal membrane and a stage II macular hole (see 4.6). Having taken into account all of the evidence submitted (from the manufacturer and the ERG), and comments received during ACD consultation, the Committee concluded that on balance the ICER was likely to be lower than £30,500 per QALY gained and therefore ocriplasmin was a cost-effective use of NHS resources for treating people with vitreomacular traction and a stage II macular hole without an epiretinal membrane.

- 4.22 The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way. No equality issues were raised during the appraisal process or at the Committee meetings, and therefore the Committee concluded that no alterations or additions to its recommendations were needed.

Summary of Appraisal Committee's key conclusions

TA297	Appraisal title: Ocriplasmin for treating vitreomacular traction	Section
Key conclusion		

<p>Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if</p> <ul style="list-style-type: none"> • an epiretinal membrane is not present <p>and</p> <ul style="list-style-type: none"> • they have a stage II full-thickness macular hole with a diameter of 400 micrometres or less and/or • they have severe symptoms. <p>The Committee understood that the treatment pathway, and therefore the use of ocriplasmin, varies depending on the presence or absence of a stage II macular hole. If a stage II macular hole is present, the Committee acknowledged that ocriplasmin would be used during the wait for surgery, without delaying surgery. However, if a stage II macular hole is not present, the Committee recognised that ocriplasmin would be offered as an alternative to surgery, or as an alternative to 'watch and wait' for people who have severe distressing symptoms but are not eligible for surgery.</p> <p>The Committee concluded that ocriplasmin was clinically and cost effective in the VMT without ERM (vitreomacular traction without an epiretinal membrane), and VMT with MH (vitreomacular traction with a stage II macular hole) subgroups.</p> <p>The Committee recognised that in the VMT with ERM (vitreomacular traction with an epiretinal membrane) subgroup, the effect of ocriplasmin was small and not statistically significant. The Committee heard from the clinical specialists that they did not consider ocriplasmin to have a place in the treatment of patients with vitreomacular traction and an epiretinal membrane because it was not clinically effective in these patients. The Committee recognised that the VMT with MH group included people with an epiretinal membrane, and taking into account the data from the VMT with ERM subgroup and the opinion of the clinical specialists it concluded that ocriplasmin was unlikely to be clinically or cost effective in people with an epiretinal membrane in any of the subgroups, including VMT with MH.</p>	<p>1.1, 4.2, 4.6, 4.12, 4.13, 4.21</p>
<p>Current practice</p>	

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee understood that vitreomacular traction is managed differently depending on whether or not a stage II macular hole is present; if a stage II macular hole is present, ocriplasmin would be used during the wait for surgery, without delaying surgery; if a stage II macular hole is not present, ocriplasmin would be used as an alternative to surgery, or as an alternative to 'watch and wait' for people who have severe distressing symptoms.</p> <p>The Committee understood that, although vitrectomy surgery is effective in resolving vitreomacular traction and the recovery time after surgery is short, the recovery is an unpleasant process for patients, and that surgery has risks and could damage the eye. The Committee concluded that an alternative treatment for vitreomacular traction would be welcomed by clinicians and patients.</p>	<p>4.2, 4.3</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee agreed with the clinical specialists that the ocriplasmin injection provided a step change in treating patients with vitreomacular traction because it provides an alternative to 'watch and wait' and/or surgery. The Committee concluded that it was innovative.</p>	<p>4.20</p>

What is the position of the treatment in the pathway of care for the condition?	The Committee understood that in UK clinical practice patients who have a stage II macular hole would be listed for surgery and ocriplasmin would be administered during the period before surgery, without delaying surgery. For patients without a macular hole, ocriplasmin would be offered as an alternative to surgery, or as an alternative to 'watch and wait' for people who have severe distressing symptoms.	4.2
Adverse reactions	The Committee understood that adverse event rates were similar between placebo and ocriplasmin and that most were non-serious, mild in intensity, and resolved, and therefore were not considered to be clinically significant.	3.11, 4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee acknowledged that all the relevant evidence was likely to have been identified by the manufacturer and that the evidence to support the clinical effectiveness was from the TG-MV-006 and TG-MV-007 trials. The Committee understood that the evidence presented by the manufacturer matched the decision problem.	3.31, 4.5
Relevance to general clinical practice in the NHS	The Committee discussed the comparator arm in the trials and noted that a placebo injection was used in the trials instead of the UK clinical practice of 'watch and wait'. The Committee concluded that the placebo injection in the clinical trials was not equivalent to 'watch and wait' and that it was plausible that the efficacy of ocriplasmin would have been greater if it had been compared with the UK clinical practice of 'watch and wait'.	4.7

Uncertainties generated by the evidence	<p>The Committee recognised 2 key uncertainties in the clinical evidence:</p> <ul style="list-style-type: none"> • The comparator in the trials was a placebo injection rather than 'watch and wait'. • Patients may have had a shorter waiting period before vitrectomy in the clinical trial than would be expected in clinical practice. <p>The Committee concluded that the efficacy of ocriplasmin may have been underestimated because of these uncertainties.</p>	4.7, 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	<p>The manufacturer presented 3 different subgroups, for which there was differential effectiveness. The Committee took into account the data from the VMT with ERM subgroup and the opinion of the clinical specialists and concluded that ocriplasmin was unlikely to be clinically effective in people with an epiretinal membrane in any of the subgroups, including VMT with MH. The Committee concluded that ocriplasmin was clinically effective in the subgroups VMT without ERM and VMT with MH, but not in the subgroup VMT with ERM, and was unlikely to be clinically effective in those in the VMT with MH subgroup who had an epiretinal membrane.</p>	4.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	<p>The Committee noted that there was a statistically significant benefit in terms of vitreomacular traction resolution and total posterior vitreous detachment at day 28 in the VMT without ERM and VMT with MH subgroups.</p>	4.5
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee considered the cost-effectiveness evidence presented in the manufacturer's submission, including the base-case incremental cost-effectiveness ratios (ICERs), the sensitivity and scenario analyses, as well as the Evidence Review Group's (ERG) critique of the manufacturer's evidence. The Committee understood that the modelling approach presented by the manufacturer was appropriate and that the assumptions and data sources were reasonable.	3.35
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee considered important areas of uncertainty in the model:</p> <ul style="list-style-type: none"> • The assumption that vitrectomy and cataract surgery would be completed separately, and that when the model accounted for combined surgery a disutility value to account for the addition of cataract removal to surgery was not added. • The cataract rate. • The macular hole vitrectomy success rate. • The metamorphopsia disutility value. • The number of optical coherence tomography and follow-up visits post-vitrectomy. • The retinal detachment and retinal tear rate. • The rate of visual decline not accounting for a macular hole. 	4.14, 4.15, 4.16, 4.17, 4.18

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee agreed with clinical specialists that the ocriplasmin injection provided a step change in treating patients with vitreomacular traction because it provides an alternative to 'watch and wait' and/or surgery. The Committee concluded that it was innovative. The Committee recognised that the benefit of this may not have been captured in the quality-adjusted life year (QALY) calculation.</p>	<p>4.20</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee understood that there was not a group of people for whom ocriplasmin was particularly cost effective. However, it recognised that ocriplasmin was not clinically effective (in terms of total posterior vitreous detachment [PVD] and vitreomacular traction resolution by day 28) for patients with vitreomacular traction and epiretinal membrane, without a stage II macular hole. In addition, it concluded, taking into account the views of clinical specialists and the data from the VMT with ERM subgroup, that ocriplasmin was unlikely to be clinically effective (in terms of total PVD and vitreomacular traction resolution by day 28) for patients with vitreomacular traction, an epiretinal membrane and a stage II macular hole. It therefore concluded that ocriplasmin was not cost effective for these groups.</p>	<p>3.8, 3.9, 4.6, 4.13, 4.21</p>

What are the key drivers of cost effectiveness?	For the VMT without ERM and VMT with ERM subgroups the model outcomes were most sensitive to the inputs determining non-surgical resolution of vitreomacular traction at 6 months and 28 days. The QALY discount rate was also an important driver for these subgroups. For the VMT with MH subgroup, the model outcomes were most sensitive to the inputs that determined non-surgical macular hole closure, cataract disutility and the change of macular hole closure post-vitreectomy.	3.26
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<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered the use of ocriplasmin to treat vitreomacular traction without an epiretinal membrane or a stage II macular hole and concluded that the ICER was likely to be no greater than £20,900 per QALY gained (as presented by the ERG). It agreed therefore that ocriplasmin was a cost-effective use of NHS resources for treating vitreomacular traction in people without an epiretinal membrane.</p> <p>The Committee considered the use of ocriplasmin to treat vitreomacular traction with an epiretinal membrane but without a stage II macular hole and recognised that ocriplasmin was not clinically effective or cost effective for these people. The Committee therefore concluded that ocriplasmin could not be considered a cost-effective use of NHS resources for treating people with vitreomacular traction and an epiretinal membrane, without a stage II macular hole.</p> <p>The Committee considered the use of ocriplasmin to treat vitreomacular traction with a stage II macular hole. The Committee agreed that the preferred assumption was to include combined cataract and vitrectomy surgery, and noted the associated ICER was approximately £30,500 per QALY gained. The Committee also considered that addressing uncertainties in the model could both increase and decrease the ICER. The Committee recognised that ocriplasmin was unlikely to be clinically effective in patients who have an epiretinal membrane and a stage II macular hole. Having taken into account all of the evidence submitted (from the manufacturer and the ERG), and comments received during consultation, the Committee concluded that on balance the ICER was likely to be lower than £30,500 per QALY gained and therefore ocriplasmin was a cost-effective use of NHS resources for treating people with vitreomacular traction and a stage II macular hole without an epiretinal membrane.</p>	<p>4.21</p>
<p>Additional factors taken into account</p>		

Equalities considerations and social value judgements	No equality issues within the scope of this appraisal were raised during the appraisal process or at the Committee meetings.	
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has vitreomacular traction and the doctor responsible for their care thinks that ocriplasmin is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing template and report to estimate the national and local savings and costs associated with implementation.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review in October 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
October 2013

7 Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Kathryn Abel

Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

Dr Daniele Bryden

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Formerly - Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler

Lay Member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Dept of Primary Care and Population Health, University College London

Dr Maria Dyban

General Practitioner, Kings Road Surgery, Cardiff

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler

Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam

Lay Member

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine

Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Dr Suzanne Martin

Reader in Health Sciences

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing and Healthcare School/Senior Clinical University Teacher, University of Glasgow

Alan Rigby

Academic Reader, University of Hull

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Tim Stokes

Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle

Lay Member

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Melinda Goodall

Technical Lead

Dr Sally Doss

Technical Adviser

Lori Farrar

Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Group:

- Edward SJ, Krause T, Trevor N, Lois N, Thurgar EJ, Barton S. Ocriplasmin for the treatment of vitreomacular traction: A Single Technology Appraisal. BMJ Technology Assessment Group, 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- ThromboGenics

II. Professional/specialist and patient/carer groups:

- Macular Society
- Royal National Institute of Blind People (RNIB)
- British and Eire Association of Vitreo Retinal Surgeons
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Pathologists

III. Other consultees:

- Department of Health
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

-
- Commissioning Support Appraisals Service
 - Department of Health, Social Services and Public Safety for Northern Ireland
 - Healthcare Improvement Scotland
 - National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on Ocriplasmin for the treatment of vitreomacular traction by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Andrew Lotery, Professor of Ophthalmology, nominated by RNIB - clinical specialist
- Ian Pearce, Consultant Ophthalmologist, nominated by Royal College of Ophthalmologists – clinical specialist
- Tim Jackson, Consultant Ophthalmic surgeon, nominated by ThromboGenics – clinical specialist
- Cathy Yelf, nominated by Macular Society - patient expert
- Linda Buxton, nominated by RNIB - patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- ThromboGenics

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Changes after publication

October 2013: dose of ocriclasmin in section 2.1 corrected from 0.125 micrograms to 0.125 mg.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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