Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

ocriplasmin, 0.5mg/0.2 mL, concentrate for solution for injection (Jetrea®)
SMC No. (892/13)

ThromboGenics NV

04 July 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

ocriplasmin (Jetrea®) is accepted for restricted use within NHS Scotland.

Indication under review: In adults for the treatment of vitreomacular traction, including when associated with macular hole of diameter less than or equal to 400 microns.

SMC restriction: patients with vitreomacular traction plus macular hole, regardless of whether they have epiretinal membrane formation, and in patients with vitreomacular traction alone (no epiretinal membrane and no macular hole).

In two randomised, controlled double-masked studies, significantly more patients treated with ocriplasmin than placebo achieved resolution of vitreomacular adhesions which may correlate with improved visual acuity.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In adults for the treatment of vitreomacular traction, including when associated with macular hole of diameter less than or equal to 400 microns.

Dosing Information

A single intravitreal injection of 125 micrograms (0.125mg) = 0.1mL of the diluted solution, administered to the affected eye.

Ocriplasmin must be prepared and administered by a qualified ophthalmologist experienced in intravitreal injections. The diagnosis of vitreomacular traction should comprise of a complete clinical picture including patient history, clinical examination and investigation using currently accepted diagnostic tools, such as optical coherence tomography.

Product availability date

26 March 2013

Summary of evidence on comparative efficacy

In the normal ageing process, the vitreous liquefies and shrinks, causing it to detach from the retina. Vitreomacular adhesions (VMA) occur when the posterior vitreous fails to detach completely and there is persistent adherence to the macula. Subsequent shrinkage of the vitreous cortex from the macula results in tangential traction, which produces vitreomacular traction (VMT). VMT causes decreased and distorted vision and is a risk factor for development of a macular hole. Persistent traction on the macula may also cause cystoid macular oedema and epiretinal membrane (ERM) formation. Symptoms may remain stable and VMT, including that associated with macular hole, can occasionally resolve spontaneously, or some patients can have worsening traction and deteriorating visual acuity.

Ocriplasmin is a truncated form of human plasmin and is a protease enzyme produced using recombinant DNA technology. It breaks down the proteins responsible for the adhesion, thereby increasing the probability of complete detachment of the vitreous from the macula. The submitting company has requested that SMC considers ocriplasmin when positioned for use in patients with VMT plus macular hole, regardless of whether they have an ERM, and in patients with VMT alone (no ERM and no macular hole). The group of patients with VMT and ERM but with no macular hole is also covered by the licence but not included in the positioning proposed in the company's submission.

The evidence supporting the marketing authorisation is from two almost identical, double-masked, randomised controlled phase III studies (TG-MV-006 and TG-MV-007).[1-4] They compared the efficacy and safety of ocriplasmin with placebo in a combined total of 652 adults with symptomatic focal VMA (defined as vitreous adhesion to the macula within a 6mm central retinal field surrounded by elevation of the posterior vitreous cortex, as seen on optical coherence tomography [OCT]), and best corrected visual acuity (BCVA) of ≤20/25 in the study eye and ≥20/800 in the non-study eye, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) acuity chart. Patients were randomised in a ratio of 3:1 (amended to 2:1 in study TG-MV-006 shortly after study initiation) to a single intravitreal injection of ocriplasmin 125

microgram/0.1mL or placebo (0.1mL of drug vehicle diluted with saline), patients were observed for six months.

The primary outcome was the proportion of patients with non-surgical resolution of focal VMA, without creation of an anatomical defect, at day 28, as assessed by masked central reading centre OCT. The primary analysis population was the full analysis set (FAS) which included all randomised patients who received treatment with study drug. Other populations analysed were the modified FAS, all randomised patients who received treatment with study drug and had symptomatic focal VMA at baseline, and the per protocol population, FAS patients without substantial protocol deviations.[2] In both studies, resolution of VMA was achieved in significantly more patients treated with ocriplasmin than placebo in all three analysis populations. Results for the FAS population are presented in table 1 for the individual studies and for the pooled population.

Table 1; proportion of patients in studies TG-MV-006, TG-MV-007 and the pooled population who achieved the primary outcome, VMA resolution at day 28 (FAS) [1]

	TG-MV-006		TG-MV-007		Pooled population	
	Ocriplasmin	**Placebo**	**Ocriplasmin**	**Placebo**	**Ocriplasmin**	**Placebo**
Non-surgical resolution of focal VMA at day 28						
Proportion (n/N)	28% (61/219)	13% (14/107)	25% (62/245)	6.2% (5/81)	27% (123/464)	10% (19/188)
Odds ratio (95% CI) p-value*	2.56 (1.32 to 5.24) 0.003		5.13 (1.97 to 17.00) <0.001		3.28 (1.93 to 5.84) <0.001	

VMA=vitreomacular adhesion; FAS=full analysis set; CI=confidence interval *p value from Fisher's exact test

The key secondary outcome was the proportion of patients with total posterior vitreous detachment (PVD) at day 28, assessed by a masked investigator using standardised B-scan ultrasonograms, and this was significant for ocriplasmin compared with placebo in both studies. Results of this and other secondary outcomes are presented in table 2 for the individual studies and for the pooled population.

Table 2; secondary outcomes for studies TG-MV-006, TG-MV-007 and the pooled population (FAS)[1-4]

Study	**TG-MV-006**		**TG-MV-007**		**Pooled population**	
	Ocriplasmin (n=219)	**Placebo (n=107)**	**Ocriplasmin (n=245)**	**Placebo (n=81)**	**Ocriplasmin (n=464)**	**Placebo (n=188)**
Total PVD at day 28						
Proportion	16%	6.5%	11%	0	13%	3.7%
Odds ratio (95% CI) p value	2.80 (1.17 to 7.74) 0.01		13.55 (2.35 to ∞) <0.001		4.27 (1.89 to 11.32) <0.001	
Vitrectomy by 6 months						
Proportion	20%	29%	15%	24%	18%	27%
Odds ratio (95% CI) p value	0.64 (0.36 to 1.12) 0.1		0.58 (0.30 to 1.15) 0.09		0.61 (0.40 to 0.94) 0.02	

FTMH closure without vitrectomy by 6 months						
Proportion	46%	16%	35%	20%	41%	17%
Odds ratio (95% CI) p value	4.46 (1.42 to 16.96) 0.005		2.10 (0.47 to 13.18) 0.35		3.45 (1.40 to 9.49) 0.004	
Improvement of ≥2 lines in BCVA at 6 months						
Proportion	30%	17%	26%	18%	NR	NR
Odds ratio (95% CI) p value	2.13 (1.16 to 4.06) 0.01		1.66 (0.85 to 3.44) 0.13		NR	
Improvement of ≥3 lines in BCVA at 6 months						
Proportion	13%	8.4%	12%	3.7%	12%	6.4%
Odds ratio (95% CI) p value	1.59 (0.70 to 4.00) 0.27		3.48 (1.03 to 18.35) 0.03		2.09 (1.08 to 4.41) 0.02	
Improvement in BCVA (ETDRS letters) from baseline to 6 months						
Mean	3.5	2.8	3.6	2.1	NR	NR

FAS=full analysis set; CI=confidence interval; PVD=posterior vitreous detachment; FTMH=full thickness macular hole; BCVA=best corrected visual acuity

Health related quality of life was assessed at baseline and at six months using the self-administered National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25), range 1 to 100, with higher scores indicating better health.[1] The difference from placebo in mean improvement at six months in VFQ-25 composite score was 2.3 points in TG-MV-006 and 3.4 points in TG-MV-007. In the pooled analysis, the difference between ocriplasmin and placebo was statistically significant for the VFQ-25 composite score: 3.4 versus 0.7; difference 2.7, 95% CI 0.7 to 4.8, p=0.007;[1] and in five out of twelve subscales: general vision, distance vision, mental health, dependency and driving[5]. A clinically meaningful improvement in the VFQ-25 composite score (based on a minimum clinically important difference of 3.6) was observed in a significantly larger proportion of the ocriplasmin group than the placebo group (36% versus 23%, p=0.0016).[6]

Sub-group analyses (one of which was post hoc) of the pooled population provide efficacy data for the populations relevant to the positioning proposed by the submitting company. In the VMT (no ERM, no macular hole) subgroup (n=266), the proportion of patients with non-surgical VMA resolution at day 28 was 30% for ocriplasmin and 7.7% for placebo (p<0.001) and in the VMT (and macular hole) subgroup (n=153), the proportion of patients was 50% versus 26% respectively (p=0.006). Results for the key secondary endpoint of proportion of patients with total PVD at day 28 were also significant for ocriplasmin versus placebo; VMT (no ERM, no macular hole) subgroup (17% versus 2.6%, p<0.001) and VMT (and macular hole) subgroup (23% versus 8.5%, p=0.033). For all other secondary endpoints differences were small but favoured ocriplasmin).[7]

A long-term, non-interventional, follow-up study recruited 24 patients who had previously participated in one of the pivotal studies.[8,9] It consisted of one patient visit to assess long term visual function including ocular history, visual acuity, ETDRS, full ophthalmologic assessment, Spectral Domain Optical Coherence Tomography (SD-OCT), and electroretinography assessment.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Safety results are from the pooled analysis of studies TG-MV-006 and TG-MV-007. It should be noted that, due to the use of a placebo intravitreal injection rather than a sham injection, the difference in adverse events between treatment groups does not demonstrate injection-related events, i.e. both treatment groups were exposed to injection-related adverse events.

A higher proportion of ocriplasmin than placebo patients experienced adverse events: 77% (356/465) versus 69% (129/187), and treatment-related adverse events: 40% (186/465) versus 21% (40/187). The incidence of serious adverse events was similar in the ocriplasmin and placebo groups: 13% (62/465) versus 13% (24/187).[2]

Most adverse events were ocular and these were reported by a significantly higher proportion of ocriplasmin than placebo patients: 68% (318/465) versus 54% (100/187), $p<0.001$. The difference was mainly attributed to adverse events known to be associated with vitreous detachment. Most adverse effects were transient and mild in severity. Adverse events that occurred significantly more often in the ocriplasmin versus placebo groups were vitreous floaters (17% versus 7.5%), photopsia (sensation of flashing lights, sparks, colours) (12% versus 2.7%), injection-related eye pain (14% versus 5.9%), blurred vision (8.6% versus 3.2%) and visual impairment (5.4% versus 1.6%).[4] No acute cataracts were reported and progression of cataract (in patients with natural lens in study eye) occurred in similar numbers of patients in the ocriplasmin and placebo groups: 8.2% and 12%, respectively.[1]

Most adverse events seem to be due to the injection procedure or to successful resolution of VMT. Severe and persistent reduction in visual function was reported in some patients. At six months post injection, 5.4% (25/465) of ocriplasmin and 3.2% (6/187) of placebo patients had ≥3-line loss in BCVA. Most of these patients had not achieved VMA resolution by day 28. It is possible that incomplete enzymatic detachment of the vitreous from the macula may cause additional tractional forces with the risk of new or enlarged macular holes which were reported for 6.7% of ocriplasmin patients versus 9.6% of placebo patients.[2]

Serious ocular adverse events occurred in 7.7% (36/465) of patients that received ocriplasmin compared with 11% (20/187) of patients that received placebo. These included macular hole 5.2% (24/465) versus 8.6% (16/187), pre-vitrectomy retinal detachment 0.4% (2/465) versus 0, and reduced visual acuity 0.6% (3/465) versus 0.5% (1/187) in the ocriplasmin and placebo groups, respectively.[1,10]

One case of lens subluxation/phacodonesis was reported in a different clinical study in adults and appears to have been possibly related to treatment with ocriplasmin.[10]

Summary of clinical effectiveness issues

Ocriplasmin is the first drug to be licensed for the treatment of VMT. Current management is to monitor patients (watch and wait) and, if the VMT deteriorates sufficiently, to remove the vitreous surgically. Vitrectomy is a major operation with substantial associated risks, including cataract, retinal tears and detachment, and is only performed when patients are at risk of severe visual disturbance and/or central blindness.[2] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, due to lack of non-surgical treatments.

The submitting company has requested that SMC considers ocriplasmin when positioned for use in two sub-populations within the licensed indication: patients with VMT plus macular hole, (regardless of ERM) and patients with VMT alone (no ERM and no macular hole).

The pivotal studies showed significant improvement for ocriplasmin over placebo for the primary outcome of VMA resolution, where treatment was only successful in approximately a quarter of patients treated with ocriplasmin compared with 10% for placebo (pooled analysis).[1] Total PVD was significantly higher for ocriplasmin than placebo, but again the treatment effect was small 13% versus 3.7%, (pooled results).[1] Non-surgical closure of macular hole at six months was considered to be significant for ocriplasmin in one of the pivotal studies and in the pooled analysis. Between 35% and 46% of patients with stage 2 macular hole (i.e. full thickness macular hole less than 400 microns) at baseline achieved closure without vitrectomy. This compares to a spontaneous closure rate for stage 2 macular hole of around 10%, and a vitrectomy closure rate of around 90%.[2] Neither study alone demonstrated a significant benefit for ocriplasmin in rate of vitrectomy at six months, although pooled results did show a small benefit that was significant. The actual rate of vitrectomy was much lower than had been anticipated at baseline at 84% (548/652).[2] Substantial improvement in the direct health outcome of improved BCVA at six months was not clearly demonstrated, but baseline BCVA was reasonably good so these results may be due to a ceiling effect as potential for improvement was limited. A significant improvement in health related quality of life was shown in the pooled analysis but not in the individual studies.[1]

The pivotal studies had several limitations. The primary outcome of VMA resolution is a surrogate endpoint which has not been validated. There is evidence that it is related to improved visual acuity, but the European Medicines Agency (EMA) noted that its clinical relevance has not yet been fully clarified although it was supported in the clinical studies programme by BCVA data. Over both studies, 16% (103/652) patients did not have an expected need for vitrectomy at baseline.[2] Visual acuity was the only symptom of VMA that was assessed in the studies and it is not known if other symptoms such as metamorphopsia and photopsia were resolved.[2] The six month follow up period is not long enough to determine avoidance of vitrectomy as some patients may still be being monitored (watch and wait). Also, any adverse events associated with vitrectomy may not be captured in this time scale. In addition, the EMA commented that since vitrectomy was performed at the discretion of the investigator, there may have been occasions when it was deferred until after the study, introducing potential bias. Patient numbers in the follow-up study were small and therefore additional data on avoidance of vitrectomy are limited.

In the pivotal studies, the comparator arm involved administration of an intravitreal placebo injection which would not be used in clinical practice. It allowed differentiation of the efficacious and adverse effects of the active drug from those of the intravitreal injection itself. It is possible

that the physical effect of injecting fluid into the vitreous could contribute to VMA resolution which may have biased against ocriplasmin and confounded the study results.[2]

For the proposed positioning clinical evidence is from subgroup analyses of the pivotal studies and is therefore less robust than for the whole study populations. Results of these analyses have been published in poster form and indicate that ocriplasmin was superior to placebo for the primary and key secondary endpoint in the two subgroups of relevance. Pre-specified subgroup analysis of the pivotal studies suggests that most benefit from ocriplasmin is gained in patients who are likely to require a vitrectomy (except for those with ERM), who have a smaller diameter focal VMA, a full thickness macular hole and poorer baseline vision.[2]

Analysis of the pivotal studies showed differences in the treatment effect of ocriplasmin according to geographical region. Fewer ocriplasmin and, more notably, placebo patients in Europe had non-surgical resolution of VMA, 23% and 4%, compared with 28% and 12% in the USA. The corresponding figures for total PVD were 6.7% and none in Europe versus 16% and 5% in the USA; and for vitrectomy were 16% in both ocriplasmin and placebo groups in Europe versus 18% and 30% in the USA.[2] Nonetheless, a modest but consistent treatment effect was shown for ocriplasmin in both studies and both regions.

Potential advantages of treatment with ocriplasmin are that it would allow earlier intervention to resolve VMA and that it involves a single intravitreal injection. However, although there is an expectation that surgery and its associated risks and complications would be avoided, this was not demonstrated at the European pivotal study sites.[2] Clinical experts consulted by SMC considered ocriplasmin to be a therapeutic advancement as it is less invasive than surgery. They viewed place in therapy as a potential alternative to surgery or to observation.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing a single intravitreal injection of ocriplasmin with a strategy of watch and wait in patients with VMT, with vitrectomy surgery an option in both treatment groups. Based on SMC expert clinical feedback the comparator is appropriate for current clinical practice in Scotland. Cost-effectiveness was explored in two sub-groups: those with VMT alone (no ERM, no macular hole), and those with VMT (plus macular hole) regardless of whether they have an ERM.

The economic model consisted of a short term decision tree model, with outcomes at 28 days and 6 months based on pooled data for ocriplasmin versus placebo injection from the two pivotal trials, and a Markov extrapolation with 3-month cycles over a lifetime horizon, which was a maximum of 37.5 years. The model consisted of 6 disease health states, based on VMT, macular hole and vitrectomy status, and within each disease state the patient could also be in one of 6 visual acuity health states in each of the study and non-study eyes (making 36 possible visual acuity health states). As there were insufficient data for each possible disease and visual acuity health state combination, regression modelling was used to determine probabilities for being in each health state. Patients are treated in a single eye, with the distribution of this being in the worse (WSE) or better seeing eye (BSE) based on the clinical trial data (so ~70% were treated in the WSE based on the pooled data). The probability of the WSE becoming the BSE during each model cycle was modelled.

Based on the clinical data used, the pooled analysis estimated that the main additional benefit of ocriplasmin treatment relative to a watch and wait strategy is faster resolution of VMT in the VMT alone (no ERM, no macular hole) sub-group (30% versus 8%) and macular hole closure in the VMT (plus macular hole) sub-group (41% versus 11%) at one month. In the VMT alone (no ERM, no macular hole) sub-group, earlier resolution of VMT translates to an improvement in short term visual acuity, reduced vitrectomy surgery (and associated complications and adverse events such as cataracts, and retinal detachment), reduced metamorphopsia symptoms and related improvements in health related quality of life. A key assumption was that the rate of decline in visual acuity over time was greater for patients without VMT resolution compared to those with VMT resolution, resulting in a continued benefit for the ocriplasmin treatment over the lifetime horizon even after vitrectomy surgery, which was assumed effective at VMT resolution, in the watch and wait strategy. The main benefit of macular hole closure in the VMT (plus macular hole) sub-group was the reduced probability of vitrectomy and associated cataract surgery. The probability of macular hole closure after vitrectomy surgery was estimated from trial dataset. The probability of a cataract requiring surgery was estimated to be 92% based on a published study for the VMT (plus macular hole) sub-group and 42.7% in the VMT (no ERM, no macular hole) sub-group. The probability of cataract surgery being performed at the same time as vitrectomy was estimated based on data requested by the company from the Information Service Division, NHS Scotland (ISD). Cataract related adverse events were from the pooled ocriplasmin phase III studies, the probability of a second vitrectomy procedure was from expert opinion and the likelihood of vitrectomy success was taken from additional follow-up information from the pivotal studies.

Utilities were estimated for the visual acuity health states from a published time trade-off study performed in the general public using contact lenses to simulate visual impairment for age related macular degeneration. As these data provide utilities based on the BSE, and treatment of the WSE does not produce equivalent utility benefits, an algorithm was developed to estimate the utility for visual acuity associated with the WSE conditional upon the BSE visual acuity state patients are in. This assumed a gain in utility from an improvement in visual acuity in the WSE is equal to 30% of the equivalent change in the BSE, which is in line with previous appraisals. Disutilities associated with cataracts, other adverse events, and metamorphopsia were also included based primarily on published data. Vitrectomy was assumed to be associated with a disutility equivalent to two weeks in the worst visual acuity health state.

Resource use for ocriplasmin administration (outpatient appointment), post ocriplasmin, watch and wait and vitrectomy surgery monitoring and OCT were estimated using expert clinical opinion. The method for obtaining this opinion was a Scottish advisory board organised by the company. The costs of vitrectomy surgery and cataract surgery appear appropriate. The costs of blindness (defined as EDTRS <35 letter score) were derived from a published study where the majority of the unit costs associated with blindness were taken from the Hospital and Community Health Services (HSCS) index.

The main results for the VMT (no ERM, no macular hole) sub-group was an incremental cost-effectiveness ratio (ICER) for ocriplasmin of £17,832 per quality adjusted life year (QALY) gained, based on an incremental cost of £2,295 and incremental QALYs of 0.129 per patient. The main driver of the QALY gain was the lifetime improvement in visual acuity over the watch and wait strategy (representing 84% of the QALY gain). In the VMT (plus macular hole) sub-group, the ICER was £24,170 per QALY gained, based on an incremental cost of £1,900 and incremental QALYs of 0.079 per patient. The main driver of the QALY gain in this group was reduced disutility from vitrectomy/cataract surgery (representing 47.5% of the QALY gain). In each sub-group there was an incremental cost of £2,656 associated with drug treatment and

administration. In the VMT alone (no ERM, no macular hole) sub-group the main cost-offsets were lower costs of blindness (-£370), and vitrectomy/cataract surgery (-£125). In the VMT (plus macular hole) sub-group the primary offsets were a lower cost of vitrectomy/cataract surgery (-£620) and adverse event treatment (-£184).

Sensitivity analysis performed demonstrated upward sensitivity in the ICER for the VMT alone (no ERM, no macular hole) sub-group to a shorter time horizon: when this is reduced to 10 and 15 years, the ICER increases to £34k/QALY and £23k/QALY respectively. When the rate of decline in visual acuity was assumed to be the same for resolved and unresolved VMT, the ICER increased to £22k/QALY. In addition, employing a different utility source increases the ICER to £26k/QALY. When the 3-month spontaneous resolution rate is increased to 2.2% and 16.5% in the extrapolation phase, the ICER increases to £19k/QALY and £36k/QALY respectively. For the VMT (plus macular hole) sub-group; an increased success rate of 95% for vitrectomy surgery increased the ICER to £30k/QALY. Employing a different source of utility increased the ICER to £30k/QALY. In addition, when the time horizon is reduced to 10 and 15 years, the ICER increases to £30k/QALY and £26k/QALY respectively.

The main weaknesses of the economic analysis were:

- There is uncertainty over the long term extrapolation phase of the model, which results in visual acuity improvements for patients treated with ocriplasmin. In previous appraisals for eye disease, the time horizon has been 10 to 15 years. When the time horizon is reduced to 10 and 15 years, the ICER increases to £34k/QALY and £23k/QALY respectively in the VMT (no ERM, no macular hole) sub-group and £30k/QALY and £26k/QALY respectively for the VMT (plus macular hole) sub-group. SMC clinical experts highlighted that the visual acuity decline could be faster for patients with severe VMT. There is some evidence that the patient population in the pivotal studies represent this cohort of severe patients; however, the difference in visual acuity decline between patients with resolved and unresolved VMT is uncertain. Assuming visual acuity decline is the same for patients with resolved and unresolved VMT increases the ICER to £22k/QALY in the VMT (no ERM, no macular hole) sub-group.

- The economic model assumes a 0% 3-month spontaneous resolution rate for the VMT (no ERM, no macular hole) sub-group if it had not occurred within the first 6 months of the study. SMC clinical experts have suggested approximately 10% of these patients could experience spontaneous resolution. Sensitivity analysis was requested to model a spontaneous resolution rate of 10% for the VMT (no ERM, no macular hole) sub-group in the extrapolation phase and the resultant ICER increased to £27k/QALY. However, it should be noted that this analysis is based on a 3-month spontaneous resolution rate of 10%, which is likely to overestimate the resolution rate in practice.

- The company was asked to provide scenario analysis to test some of the sensitivities in combination. The scenario analysis tested a 15-year time horizon, 3-month spontaneous resolution rate of 2.2%, and a success rate of vitrectomy of 95%. This resulted in an ICER for the VMT (no ERM no macular hole) sub-group of £26k/QALY, and for the VMT (plus macular hole) sub-group the ICER was £32k/QALY. This was considered by SMC to be a more realistic analysis.

Despite the weaknesses highlighted above, the scenario analysis provided reassurance about the cost-effectiveness of ocriplasmin when some of the key uncertainties were combined. As such, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified patient groups.

- A joint submission was received from the Royal National Institute of Blind People (RNIB) and the Macular Society (MS), which are both registered charities.
- RNIB has received some pharmaceutical company funding in the past two years. MS has received no pharmaceutical company funding.
- Vitreomacular traction (VMT) may lead to permanent sight loss and can affect the central vision if not treated.
- People living with VMT are at risk of loss of employment and loss of independent mobility including inability to drive. Normal daily life can be affected including cooking safely and taking medication appropriately. There can be a loss of confidence and self-esteem, which may lead to clinical depression.
- Living with VMT can also place demands on carers and spouses who may have to give up work.
- Current treatment is “watchful waiting” for standard cases and eye surgery (vitrectomy) for more severe cases. Vitrectomy can be effective but may also have a number of significant side effects e.g. development of cataracts.
- Ocriplasmin as a treatment option may reduce the anxiety caused by ‘watchful waiting’, avoid invasive eye surgery and the associated period of post-operative recovery.

Additional information: comparators

There is no pharmacological comparator. Current practice is medical management, watch and wait, until the risk to sight outweighs the risk of vitrectomy. Ocriplasmin would be used at an earlier stage than vitrectomy. If treatment with ocriplasmin was unsuccessful, then vitrectomy would still be necessary.

Cost of relevant comparators

Drug	Dose Regimen	Cost (£)
Ocriplasmin	**125 microgram intravitreal injection to affected eye**	**2,500**

Cost from MIMS on 24 April 2014.

Additional information: budget impact

The submitting company provided a separate budget impact template for the VMT (no ERM) and VMT (plus macular hole) sub-groups.

VMT (no ERM, no macular hole) subgroup: The submitting company estimated there to be 39 patients eligible for treatment with ocriplasmin in years 1 and 2 rising to 40 patients from year 3 onwards with an estimated uptake rate of 10% in year 1 and 40% in year 5.

The gross medicines budget impact was estimated to be £10k in year 1 and £43k in year 5. No other medicines were assumed to be displaced so the net medicines budget impact was estimated to be £10k in year and £43k in year 5.

VMT (plus macular hole) subgroup: The submitting company estimated there to be 182 patients eligible for treatment with ocriplasmin in year 1 and 188 patients in year 5 with an estimated uptake rate of 10% in year 1 and 40% in year 5.

The gross medicines budget impact was estimated to be £48k in year 1 and £200k in year 5. No other medicines were assumed to be displaced so the net medicines budget was estimated to be £48k in year 1 and £200k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Stalmans P, Benz M, Gandorfer A et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. New England Journal of Medicine. 2012; 367(7): 606-15

2. European Medicines Agency European Public Assessment Report for ocriplasmin EMEA/H/C/002381/0000 17 January 2013

3. *Commercial in Confidence*

4. *Commercial in Confidence*

5. Correspondence relating to Stalmans P, Benz M, Gandorfer A et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. New England Journal of Medicine. 2012; 367; 2053

6. Jackson TL, Verstraeten T, Duchateau L. Visual function response with ocriplasmin. BEAVRS Dublin. 2012 Nov;(Abstract).

7. Narendran et al. Baseline Characteristics across Clinically-Relevant Sub-groups of Vitreomacular Traction Patients Enrolled in Ocriplasmin Phase 3 Randomised controlled Trials. Presented at 13th AMD and Retina Congress Dublin 2013

8. www.clinicaltrials.gov [NCT01287988]

9. *Commercial in Confidence*

10. Ocriplasmin (Jetrea®) Summary of product characteristics. Alcon Laboratories (U.K) Limited Last updated 26 April 2013

This assessment is based on data submitted by the applicant company up to and including 13 June 2014.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the Monthly Index of Medical Specialities (MIMS). SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.