# Prior Authorization Review Panel
## MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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**Type of Submission – Check all that apply:**

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0848 Ocriplasmin (Jetrea)**

This CPB has been revised to simplify the criteria for ocriplasmin (Jetrea) for vitreomacular traction.

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<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>Bernard Lewin, M.D.</td>
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Revised July 22, 2019
Ocriplasmin (Jetrea)

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers ocriplasmin (Jetrea) medically necessary for the treatment of symptomatic vitreo-macular adhesion (VMA) of at least 6 weeks duration when the member has a best corrected visual acuity of 20/25 or less in the affected eye.

Aetna considers continuation of ocriplasmin therapy medically necessary for persons who meet criteria listed above.

Aetna considers ocriplasmin experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Age-related macular degeneration
- Catheter-related thrombosis
- Coronary artery thrombosis
- Diabetic retinopathy
- Foveal schisis (foveoschisis)
- Mobilization of hematopoietic progenitor cells
- Peripheral arterial occlusion
- Retinal vein occlusions
- Stage 3 and stage 4 macular holes (stage 3 -- macular holes greater than 400 μm associated with partial vitreo-macular separation); stage 4 -- complete vitreous

Policy History

Last Review
10/29/2019
Effective: 05/31/2013
Next Review: 09/24/2020

Definitions

Additional Information

Clinical Policy Bulletin
Notes
separation from the entire macula and optic disc)

- Stroke
- Surgical adjunct to vitrectomy
- Vitreous hemorrhage.

Dosing Recommendations

Ocriplasmin is available as Jetrea in single-use glass vials containing 0.5mg/0.2mL solution for intravitreal injection.

The prescribing information of Jetrea notes the following regarding its dosage and administration:

- Must dilute before use.
- For single use ophthalmic intra-vitreal injection only.
- The recommended dose is 0.125 mg (0.1 ml of the diluted solution) administered by intra-vitreal injection to the affected eye once as a single dose.

The prescribing information states that repeated administration of Jetrea in the same eye is not recommended.

Source: Prescribing Information.

Background

Vitreo-macular adhesion (VMA) is a condition in which the vitreous gel of the eye adheres to the retina in an abnormally strong manner. As the eye ages, it is common for the vitreous gel to separate from the retina. However, if this separation is incomplete (i.e., there is still an adhesion), this can create pulling forces on the retina, which may result in subsequent loss or distortion of vision. Vitreo-macular adhesion by itself is not dangerous, but the resulting vitreomacular traction (VMT) can result in macular damage. The current treatment for VMA is vitrectomy that entails the surgical removal of the vitreous gel from the eye. More recently, agents such as plasmin and microplasmin (also known as ocriplasmin), administered as a single intra-vitreal injection, have been employed as non-invasive treatment of VMA.
Ocriplasmin (molecular weight of 27.2 kDa), a recombinant protease, is a truncated form of human plasmin obtained from microplasminogen produced in a Pichia pastoris expression system by recombinant DNA. Ocriplasmin is purported to exert proteolytic effects on fibrinogen, fibronectin and, to a lesser extent, laminin and collagen, each of which is a component of VMA. Ocriplasmin has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) (e.g., laminin, fibronectin and collagen), thereby dissolving the protein matrix responsible for the vitreomacular adhesion (VMA).

Jetrea (ocriplasmin) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of symptomatic vitreomacular adhesion. The safety and effectiveness of ocriplasmin for the treatment of patients with VMA has been evaluated in several clinical trials.

In a multi-center, prospective, uncontrolled, dose-escalation, phase I/II clinical trial, de Smet et al (2009) evaluated the safety and preliminary efficacy of 4 doses and several exposure times of intra-vitreal microplasmin given before pars plana vitrectomy (PPV) for VMT maculopathy. A total of 60 patients were enrolled into 6 successive cohorts. A single intra-vitreal injection of microplasmin at 1 of 4 doses (25, 50, 75, or 125 microg in 100 microl) was administered 1 to 2 hours, 24 hours, or 7 days before planned PPV. For safety, a complete ophthalmologic examination, fundus photography, fluorescein angiography, Humphrey visual fields, and electrophysiology were carried out; for efficacy, PVD induction as assessed by B-scan ultrasound and ease of PVD induction at the time of vitrectomy were performed. The use of microplasmin led to a progressively higher incidence of PVD induction on ultrasonography with increasing time exposure. A PVD before surgery was observed with 25 microg microplasmin in 0, 2, and 5 patients with increasing exposures (2 hours, 24 hours, 7 days). With increasing dose, a PVD before surgery was observed by ultrasound as follows: 25 microg, n = 0; 50 microg, n = 1; 75 microg, n = 2; 125 microg, n = 3. However, at surgery, with a 125-microg dose, these patients had a discontinuous layer of vitreous present on the retinal surface resulting from the induction of an anomalous PVD in the form of vitreoschisis. One retinal detachment developed shortly after administration of microplasmin; 2 developed after surgery. There were no other safety concerns. The authors concluded that results from this initial clinical trial evaluating intra-vitreal microplasmin showed the drug to be well-tolerated and capable of inducing a pharmacologic PVD in some patients.

In a randomized, double-masked, phase II clinical trial, Stalmans et al (2010) evaluated the ability of a single or repeated injection of microplasmin to release VMT (n = 6). Patients in each of the 4 cohorts were randomized (4:1) to active treatment or sham injection. In the first 3 cohorts, increasing doses of microplasmin (75, 125, and 175 microg) were administered. In the 4th cohort, an initial injection of 125 microg microplasmin or sham was administered followed 1 month later by an injection of 125 microg microplasmin if no release of adhesion occurred. A 3rd
dose was injected 4 weeks later if there was still no release of adhesion. Within 28 days of sham, 75, 125, and 175 microg microplasmin administrations, non-surgical resolution of VMA was observed in 8, 25, 44, and 27 % of the patients, respectively. When the 125-microg dose was repeated up to 3 times, adhesion release was observed in 58 % of patients 28 days after the final injection. The authors concluded that these findings provided support for the potential of microplasmin as a non-surgical treatment for VMA.

In a phase II, multi-center, placebo-controlled, double-masked, parallel-group, dose-ranging clinical trial, Benz et al (2010) evaluated the safety and effectiveness of a pre-operative intra-vitreal injection of microplasmin in patients scheduled for vitrectomy. A total of 125 patients scheduled for PPV, primarily for treatment of either VMT or macular hole were included in this study. A single intra-vitreal injection of either microplasmin at 1 of 3 doses (25 microg, 75 microg, or 125 microg in 100 microl) or placebo injection was administered 7 days before PPV. Main outcome measures included presence or absence of PVD at the time of PPV, progression of PVD, and resolution of vitreo-macular interface abnormality precluding the need for PPV.

Rates of total PVD at the time of surgery were 10 %, 14 %, 18 %, and 31 % in the placebo group (n = 30), 25-microg (n = 29), 75-microg (n = 33), and 125-microg microplasmin groups (n = 32), respectively. The secondary end point resolution of vitreo-macular interface abnormality precluding the need for vitrectomy at the 35-day time point was observed at rates of 3 %, 10 %, 15 %, and 31 % in the placebo, and the 25-microg, the 75-microg, and the 125-microg microplasmin groups, respectively. At the 180-day time point, the equivalent rates were 3 %, 7 %, 15 %, and 28 %, respectively. The authors concluded that microplasmin injection at a dose of 125 microg led to a greater likelihood of induction and progression of PVD than placebo injection. Patients receiving microplasmin were significantly more likely not to require vitrectomy.

In 2 multi-center, randomized, double-blind, phase III clinical trials, Stalmans et al (2012) compared a single intra-vitreal injection of ocriplasmin (125 microg) with a placebo injection in patients with symptomatic VMA. The primary end point was resolution of VMA at day 28. Secondary end points were total PVD and non-surgical closure of a macular hole at 28 days, avoidance of vitrectomy, and change in best-corrected visual acuity (BCVA). Overall, 652 eyes were treated: 464 with ocriplasmin and 188 with placebo. Vitreo-macular adhesion was resolved in 26.5 % of ocriplasmin-injected eyes; and in 10.1 % of placebo-injected eyes (p < 0.001). Total PVD was more prevalent among the eyes treated with ocriplasmin than among those injected with placebo (13.4 % versus 3.7 %, p < 0.001). Non-surgical closure of macular holes was achieved in 40.6 % of ocriplasmin-injected eyes, as compared with 10.6 % of placebo-injected eyes (p < 0.001). The BCVA was more likely to improve by a gain of at least 3 lines on the eye chart with ocriplasmin than with placebo. Ocular adverse events (e.g., vitreous floaters, photopsia, or injection-related eye pain -- all self-reported -- or conjunctival hemorrhage) occurred in 68.4 % of ocriplasmin-injected eyes and in 53.5 % of placebo-injected eyes (p <
0.001), and the incidence of serious ocular adverse events was similar in the 2 groups (p = 0.26). The authors concluded that intra-vitreal injection of ocriplasmin resolved VMT and closed macular holes in significantly more patients than did injection of placebo and was associated with a higher incidence of ocular adverse events, which were mainly transient.

On October 18, 2012, the Food and Drug Administration (FDA) approved ocriplasmin (Jetrea) for the treatment of symptomatic VMA. The recommended dosage of ocriplasmin is 0.125 mg (0.1 ml of the diluted solution) administered by intra-vitreal injection to the affected eye once as a single dose. The most commonly reported adverse reactions (greater than or equal to 5 %) in patients treated with ocriplasmin were blurred vision, conjunctival hemorrhage, eye pain, macular hole, photopsia, reduced visual acuity, retinal edema, visual impairment, and vitreous floaters.

**Warnings and precautions:**

- Each vial of Jetrea (ocriplasmin) should only be used to provide a single injection for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, and injection needles should be changed before Jetrea (ocriplasmin) is administered to the other eye, however, treatment with Jetrea (ocriplasmin) in the other eye is not recommended within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye.
- Repeated administration of Jetrea (ocriplasmin) in the same eye is not recommended.
- Decreased Vision A decrease of ≥ 3 line of best corrected visual acuity (BCVA) was experienced by some patients treated with Jetrea (ocriplasmin) in controlled trials. The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately.
- Intravitreal Injection Procedure Associated Effects Intravitreal injections are associated with intraocular inflammation / infection, intraocular hemorrhage and increased intraocular pressure (IOP). In the controlled trials, intraocular inflammation occurred in some patients injected with Jetrea (ocriplasmin). Most of the post-injection intraocular inflammation events were mild and transient.
- Dyschromatopsia Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with Jetrea (ocriplasmin). In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).
Ocriplasmin has also been investigated for other uses in laboratory and clinical studies, including mobilization of hematopoietic progenitor cells, as a surgical adjunct to vitrectomy, as well as treatment of catheter-related thrombosis, coronary artery thrombosis, exudative age-related macular degeneration, peripheral arterial occlusion, ischemic stroke, and vitreous hemorrhage. However, there is currently insufficient evidence to support the use of ocriplasmin for these indications.

Tjwa et al (2008) stated that the role of proteinases in the mobilization of hematopoietic progenitor cells (HPCs) after granulocyte colony-stimulating factor (G-CSF) remains unclear. These researchers reported that genetic loss of the plasminogen activator inhibitor Pai-1 or of the plasmin inhibitor alpha2-antiplasmin increases HPC mobilization in response to G-CSF. Moreover, thrombolytic agents (e.g., microplasmin and tenecteplase) enhance HPC mobilization in mice as well as humans. The authors concluded that these findings identified a novel role for plasmin in augmenting HPC mobilization in response to G-CSF. Well-designed studies are needed to ascertain the clinical value of microplasmin in the mobilization of HPCs.

In an open-label, ascending-dose, pilot study, Verhamme et al (2009) examined the safety and effectiveness of intra-catheter microplasmin bolus administration for the restoration of catheter function in long-term venous access catheter thrombosis. This study enrolled 31 subjects. Two doses of microplasmin were evaluated: 5 mg and 8 mg administered via a 2-ml intra-catheter bolus injection in 10 and 21 patients, respectively. Catheter function was evaluated 30 minutes after the first bolus administration. In case of incomplete catheter function restoration, a second bolus was administered with re-assessment of catheter function 30 minutes thereafter. After the first bolus, complete restoration of catheter withdrawal function was observed in 5 out of 10 (50 %) and 14 of out 21 (66 %) subjects treated with 5-mg and 8-mg of microplasmin, respectively; and in 8 out of 10 (80 %) and 18 out of 21 (86 %) subjects after a second administration of microplasmin. No bleeding complications, nor other adverse events, were related to microplasmin. The authors concluded that in this pilot trial, microplasmin restored catheter function in a safe and effective way. These preliminary findings need to be validated by well-designed studies.

In a multi-center, double-blind, randomized, placebo-controlled phase II clinical trial, Thijs and colleagues (2009) tested the tolerability of microplasmin in patients with acute ischemic stroke. A total of 40 patients with ischemic stroke were treated with either placebo or microplasmin between 3 and 12 hours after symptom onset in a dose-finding design. Ten patients received placebo, 6 patients received a total dose of 2 mg/kg body weight, 12 patients received a total dose of 3 mg/kg, and 12 patients received a total dose of 4 mg/kg. These investigators studied the pharmacodynamics of microplasmin and its effect on the clinical and hemodynamic parameters of the patients. Magnetic resonance imaging was used as a surrogate marker and
Matrix metalloproteinases serum concentrations were used as markers of neurovascular integrity. The study was under-powered to detect clinical efficacy. Microplasmin induced reversible effects on markers of systemic thrombolysis and neutralized alpha(2)-antiplasmin by up to 80%. It was well-tolerated with 1 of 30 treated patients developing a fatal symptomatic intra-cerebral hemorrhage. No significant effect on re-perfusion rate or on clinical outcome was observed. Matrix metalloproteinase-2 levels were reduced in microplasmin-treated patients. The authors concluded that microplasmin was well-tolerated and achieved neutralization of alpha(2)-antiplasmin. Moreover, they stated that further studies are needed to determine whether microplasmin is an effective therapeutic agent for ischemic stroke.

Dommke et al. (2010) examined the in-vitro fibrinolytic properties of microplasmin and its thrombolytic efficacy in a canine model of coronary artery thrombosis. The amidolytic and fibrinolytic activity of recombinant microplasmin was compared with natural human plasmin. Animals were randomly assigned to 1 of 6 treatment regimens, each with 5 animals per cohort. Four treatment groups received an intravenous bolus of microplasmin followed by an intravenous infusion of microplasmin for 1 hour (1 mg/kg + 1.5 mg/kg/hr with or without abciximab or 2 mg/kg + 3 mg/kg/hr). In 2 treatment groups, microplasmin was administered via an intra-coronary route. Bolus administration was followed by a 1-hour infusion if coronary flow was incompletely restored after the initial bolus administration (1 mg/kg + 1.5 mg/kg/hr or 2 mg/kg + 3 mg/kg/hr, respectively). The thrombolytic efficacy was documented by repeated angiographies and the coronary perfusion was assessed with the Thrombolysis in Myocardial Infarction (TIMI) grading. No significant differences between plasmin and microplasmin were observed with respect to the catalytic efficiencies towards the synthetic chromogenic substrates S-2403 or S-2444. The concentration required for 50% lysis of purified fibrin clots in 3 hours, was approximately 100 nM for microplasmin compared to 20 nM for natural plasmin. Intravenous bolus administration of microplasmin restored TIMI 3 coronary flow in 0/5, 0/5, 1/5 and 2/5, respectively, whereas intra-coronary bolus administration restored TIMI 3 coronary flow in 1/5 and 4/5 (1 mg/kg and 2 mg/kg, respectively) (ANOVA p < 0.05). Thrombolysis in Myocardial Infarction 3 coronary flow was obtained in 0/5, 2/5, 2/5 and 3/5, respectively, during subsequent intravenous administration and in 5/5 and 4/5 in case of intra-coronary administration (ANOVA p < 0.05). When compared to natural plasmin, the catalytic efficiency of microplasmin towards chromogenic substrates was similar, but the fibrinolytic potency of microplasmin towards fibrin clots was lower.

In an open-label, dose-ascending, single-center, phase IIa study, Verhamme et al. (2012) examined the safety and effectiveness of catheter-directed thrombolysis with microplasmin for infra-inguinal arterial or bypass occlusions. Patients who presented with acute occlusions were subsequently treated with an intra-thrombus infusion of 5 ascending doses of microplasmin: 0.3 mg/kg/hr for 4 hours; 0.45 mg/kg/hr for 4 hours; 0.6 mg/kg/hr for 4 hours; 0.9 mg/kg/hr for 4 hours or 0.6 mg/kg/hr for 6 hours. Repeat angiograms were obtained to assess the degree of
clot lysis. The primary outcome was complete thrombolysis defined as greater than 95% thrombus volume reduction at the end of the microplasmin infusion. Safety evaluation included bleedings, adverse events and coagulation biomarkers. Complete thrombolysis was obtained in 3 of the 19 treated patients at the end of microplasmin infusion. Thrombus volume reduction between 50% and 95% was achieved with all dosing regimens. Clinically significant distal embolization occurred in 8 patients; 1 major and 2 non-major bleedings occurred. Microplasmin depleted alpha 2-anti-plasmin and decreased fibrinogen. The authors concluded that intra-thrombus infusion of microplasmin for 4 or 6 hours resulted in significant clot lysis. Distal embolization appeared the most important limitation.

Tsui et al (2012) noted that fibronectin and laminin are clinically relevant plasmin receptors in the eye. Located at the vitreo-retinal interface, they are cleaved by ocriplasmin. A series of clinical trials to study ocriplasmin for the treatment of vitreo-retinal diseases including exudative age-related macular degeneration are underway. The results are promising and may impact patient care.

Gad Elkareem and de Smet (2014) stated that microplasmin is known to alter the structure of the vitreous gel. These researchers evaluated its ability to enhance clearance of an experimentally-induced vitreous hemorrhage, and compared it to ovine hyaluronidase. In this animal study, a total of 25 rabbits were divided into 5 groups: rabbits in groups 1 to 3 were treated with 25, 75 and 125 microg microplasmin, respectively; rabbits in group 4 were treated with 55 IU of hyaluronidase, while rabbits in group 5 were treated with normal saline (control). Eyes were injected in the mid-vitreous with 0.05 ml of autologous blood obtained from the marginal ear vein. One week later, all the groups were injected with the test solution injected in mid-vitreous as stated above. Clearance of the vitreous hemorrhage was assessed weekly by indirect ophthalmoscopy for 8 weeks. Microplasmin-treated eyes showed a significant clearance of the vitreous hemorrhage in a dose-dependent fashion, where group 3 (125 microg) had the highest clearance rate in comparison with control eyes. Hyaluronidase-treated eyes showed a similar clearance rate as group 3. In addition, group 3 showed a complete PVD, which did not develop in hyaluronidase-treated eyes. The authors concluded that microplasmin may be a useful agent to accelerate the clearance of vitreous hemorrhage.

Wong and Capone (2013) discussed the potential role of ocriplasmin as a surgical adjunct to vitrectomy in pediatric vitreo-retinopathies. These investigators performed a literature review of the laboratory and clinical evidence to-date for the use of both autologous plasmin enzyme as an adjunct to vitrectomy and more recently recombinant ocriplasmin as monotherapy for focal VMT in adults. Autologous plasmin enzyme is currently being used as a surgical adjunct to vitrectomy, with supporting levels 2 and 3 published evidence in a range of pediatric vitreo-retinopathies including stage-5 retinopathy of prematurity and congenital X-linked retinoschisis. The
availability of autologous plasmin enzyme is limited. In recent phase III clinical trials, intra-vitreal ocriplasmin versus sham injection resulted in resolution of focal VMT in 27% versus 10% (p < 0.001, n = 652). The authors concluded that ocriplasmin may potentially be used as a surgical adjunct to vitrectomy in place of autologous plasmin enzyme. A phase II, randomized, placebo-controlled surgical trial is underway to assess this.

Jackson et al (2013) noted that symptomatic VMA describes symptomatic loss of visual function as a result of vitreous traction at the macula. Symptomatic VMA (sVMA) can occur in isolation as VMT, which may lead to the development of a macular hole, or it may occur alongside epiretinal membrane. It is likely to be associated with age-related macular degeneration and possibly diabetic maculopathy, although this is less certain. The treatment depends largely on the cause, but options include observation, vitrectomy, and pharmacologic vitreolysis. Small uncontrolled trials have also explored the use of an intra-vitreal gas bubble as a means of releasing VMA. If all cases of sVMA are considered together, then the burden of illness is substantial, with a prevalence of approximately 0.35 per 100 population (excluding epiretinal membrane). Furthermore, there may be many more cases of undiagnosed sVMA. The authors concluded that the recent introduction of ocriplasmin is likely to increase interest in sVMA. The authors concluded that clinical trials suggested that it has a role in the treatment of VMT and stages 1 to 3 macular holes; but not primarily as a treatment of epiretinal membrane. Moreover, they stated that its role in other diseases associated with VMA remains to be determined.

de Smet and Castilla (2013) noted that diabetic retinopathy (DR) is a serious public health concern. Vision impairment follows from intra-ocular vascular proliferation known as proliferative DR (PDR) and/or from diabetic macular edema (DME). Clinical acumen and a recent meta-analysis of published studies suggested that the presence of a posterior vitreous detachment (PVD) reduces the risk of developing PDR, and has a favorable impact on DME. Pharmacologic vitreolysis by ocriplasmin or other agents may provide a minimally invasive method of achieving a PVD. If demonstrated in appropriate clinical studies including randomized trials, it would provide an interesting approach to prevent advanced and blinding stages of DR, particularly in areas where access to care is limited. These investigators reviewed the current epidemiology of DR as well as the role of the vitreous and its separation from the retina known as a PVD in DR based on a recent meta-analysis of published literature regarding the contribution of complete, partial or absent PVD to PDR and DME. The principles underlying vitreolysis and the induction of PVD were reviewed as well as the challenges faced by a pharmacologic approach. The results of clinical trials on the use of ocriplasmin were analyzed regarding its possible use in DR. They stated that ocriplasmin has the ability to liquefy the vitreous and induce a PVD in a statistically significant number of patients. However, current studies on patients with vitreo-macular adhesion and traction suggested that the majority of patients would not achieve a PVD with a single injection. As shown in the meta-analysis, a complete PVD is needed to significantly
reduce the risk of PDR, while a partial PVD may worsen the prognosis. If a strategy can be developed that insures a complete PVD within an appropriate time interval, the prevention of PDR might become a realistic target for ocriplasmin or other vitreolytic agents. In DME, release of traction, whether complete or partial, is associated with a reduction in DME, which in several cases has resulted in improved vision. While no studies have been conducted on the use of ocriplasmin or other vitreolytic agents in DR, a few studies using plasmin indicated that it is likely to have a beneficial effect in DME. The authors concluded that based on the information available, randomized clinical trials would be needed to evaluate the clinical relevance of ocriplasmin and other potential vitreolytic agents in both forms of DR. Such trials could determine the effectiveness of this strategy as compared to prophylactic laser particularly in high-risk populations. Moreover, they noted that new follow-up and treatment strategies would also be needed should initial studies be encouraging.

Khoshnevis and Sebag (2015) stated that with increased knowledge about the origins and pathophysiology of vitreo-retinal disorders -- and, in particular, the central role of anomalous posterior vitreous detachment in vitreo-maculopathies -- a paradigm shift from surgery to pharmacotherapy is taking place with the development of pharmacologic vitreolysis. The first approved agent for pharmacologic vitreolysis therapy is ocriplasmin, a truncated form of the non-specific serine protease plasmin. A total of 12 studies comprise the current ocriplasmin clinical trial program, demonstrating the safety and effectiveness of a single intra-vitreal injection of ocriplasmin for the treatment of patients with symptomatic VMA or VMT, including patients with macular holes. Although post-approval implementation of ocriplasmin in clinical practice has shown success rates of up to 78 %, there have been recent case reports of acute, transient visual dysfunction. There are thus new initiatives to further refine clinical indications for case selection and to identify possible untoward effects. Although more studies are warranted, it appears that ocriplasmin offers a good alternative to surgery. The future lies in pharmacologic vitreolysis, and the future of pharmacologic vitreolysis lies in prevention. The authors concluded that long-term studies are needed to define a role for pharmacologic vitreolysis, in particular with ocriplasmin, in the prevention of progressive diabetic retinopathy and age-related macular degeneration (ARMD).

Foveal Schisis

Patel and Morse (2015) reported a case of foveal schisis in X-linked retinoschisis treated with ocriplasmin. A 27-year old man with X-linked retinoschisis was treated with a single intra-vitreal injection of ocriplasmin. After injection, a posterior vitreous detachment was induced and the macular schisis cavity resolved at 1 week. Central macular thickness on optical coherence tomography (OCT) decreased from 731 μm to 185 μm, VA remained unchanged, and there were no adverse events. However, the macular schisis cavity recurred at 1 month. The authors
concluded that this was the first reported case of using ocriplasmin to treat foveal schisis in X-linked retinoschisis. They noted that although VMT was relieved, the schisis cavity recurred shortly after initial closure.

Macular Holes

Macular holes can be categorized into 4 stages: (Lowth, 2016)

Stage 1a: Seen as a yellow spot. This is not specific for macular hole -- can be associated with central serous chorioretinopathy, cystoid macular edema, and solar maculopathy

Stage 1b: Occult hole -- doughnut-shaped yellow ring (approximately 200 to 300 μm) centered on the foveola.

Stage 2: Full thickness macular hole of less than 400 μm

Stage 3: Macular holes greater than 400 μm associated with partial vitreo-macular separation

Stage 4: Complete vitreous separation from the entire macula and optic disc.

Visual acuity of individuals with stage 1 macular holes is typically minimally affected. Approximately 50% of holes progress to stage 2. Generally, VA decreases with increasing size of the hole and stabilizes at 20/200 to 20/400 for stage 3 or 4 macular holes. Vitrectomy with gas tamponade has been used for treating macular holes. In general, vitrectomy is not recommended for stage 1 macular holes; however, it is recommended for stage 2, stage 3, and stage 4 macular holes.

Casswell et al (2014) stated that ocriplasmin has been approved for the treatment of symptomatic VMA. These investigators reported the case of a 63-year old woman who presented with blurred vision in the left eye and a BCVA of 6/18. Optical coherence tomography revealed VMA with an underlying macular hole and she subsequently underwent a left intravitreal ocriplasmin injection. One week after the injection, VMA had been released but with enlargement of the macular hole and a drop in her BCVA to 6/60. This persisted at 1 month after the injection. The authors concluded that it is important to warn patients that ocriplasmin may lead to an enlargement of their macular hole with resultant loss in VA.

Lommatzsch et al (2014) reported their first experience with ocriplasmin in clinical practice. The indication for intra-vitreal therapy with ocriplasmin was provided for symptomatic VMT or macular hole with VMT in 20 patients since March 2013. Surgery was planned in cases with remaining
symptoms. Before intra-vitreal injection, these investigators performed SD-OCT. Best visual acuity was evaluated pre-operatively, 7 and 28 days after treatment and finally every month in 14 treated eyes; spectral-domain OCT (SD-OCT) images were analyzed before treatment and later on with every follow-up examination. In addition to functional and morphological changes, these researchers analyzed all side effects. The mean BCVA at the beginning of treatment was 0.3 and 0.4 before injection. The indications for treatment were as follows: symptomatic VMT in 10 patients and 4 patients suffering from full thickness macular hole (stage 2). In 3 patients spontaneous regression of VMT could be observed with increasing of vision from 0.3 to 0.5. In 1 patient his macular hole was closed and BCVA increased from 0.2 to 0.6 within 7 days. Two patients showed significant enlargement of their macular holes after 7 days and finally underwent surgery. A massive cystoid macular edema occurred in 1 patient. No change in the SD-OCT image could be observed 28 days after treatment. The mean VA improved to 0.6 during a follow-up period of 90 days. Photopsia and disturbing vitreous opacities up to 28 days post-injection could be regarded as minor side effects. The authors concluded that their first investigation with intra-vitreous injection of ocriplasmin was to confirm the presumed therapeutic effect in patients suffering from VMT. Small macular holes could frequently be closed. The possibility of special side effects must be taken in consideration just as the possibility of spontaneous improvement before performing intra-vitreal injection with ocriplasmin. They stated that further prospective studies are needed to ascertain the effectiveness of intra-vitreal ocriplasmin injections.

Miller et al (2015) reviewed clinical and structural outcomes of ocriplasmin for treatment of stage 2 macular holes. These investigators performed a retrospective review of the first patients with stage 2 macular holes to be treated with ocriplasmin at Massachusetts Eye and Ear Infirmary. All patients were imaged with SD-OCT. A total of 8 patients with stage 2 macular holes received a single injection of 125 μg of ocriplasmin. One patient (12.5 %) demonstrated macular hole closure. The posterior hyaloid separated from the macula in 6 eyes (75 %). All 7 holes that remained open showed enlargement in hole diameters (narrowest, apical, and basal) at 1 week and 1 month. All 7 were successfully closed with surgery. Ellipsoid zone disruptions were observed by OCT in 4 eyes (50 %) and persisted throughout follow-up (more than 6 months on average). The authors concluded that in early clinical results, the authors found a lower macular hole closure rate with ocriplasmin than previously reported. Enlargement was observed in all holes that failed to close with ocriplasmin. These investigators found ellipsoid zone disruptions that persisted through 6 months of follow-up after ocriplasmin injection. They stated that further work is needed to investigate the cause for these ellipsoid zone changes.

In a retrospective, single-center, consecutive interventional case-series study, Hager and colleagues (2015) evaluated the anatomical outcome of patients after vitrectomy due to persisting symptomatic VMT, including full-thickness macular holes (FTMHs) of less than 400 μm, after ocriplasmin treatment. Patients were treated with a single intra-vitreal injection of
ocriplasmin. Main outcome measures included resolution of VMT, closure of FTMH and anatomical outcome of vitrectomy after unsuccessful treatment with ocriplasmin. A total of 5 patients were treated with ocriplasmin injection; VMT persisted in all but 1 case; 4 patients underwent PPV for treatment of persistent VMT and FTMH (n = 2, size of macular hole less than 400 µm) in SD-OCT. Full-thickness macular holes were closed in both cases within the first week post-operatively. After PPV, in 3 eyes newly developed subretinal fluid was detected, which persisted up to several months post-operatively. The authors concluded that data on ocriplasmin remain controversial. They reported on 4 cases with resolution of VMT following PPV after unsuccessful ocriplasmin treatment. Newly developed subretinal fluid has been described after ocriplasmin treatment, predominantly in cases with resolution of VMT. These researchers also detected this newly developed subretinal fluid after vitrectomy, which persisted for several weeks up to 7 months in 2 cases with FTMHs. This may be attributable to loosening of the photoreceptor complex due to enzyme activity of ocriplasmin. They stated that long-term effects of ocriplasmin are still to be evaluated using SD-OCT.

Quezada-Ruiz et al (2015) reported their initial experience with intra-vitreal ocriplasmin (IVO) and described outer retina reflectivity changes observed on SD-OCT after IVO injection in patients with VMT with or without macular holes (MHs). These researchers performed a consecutive retrospective review of patients with VMT and MH who were treated with IVO. Patients underwent complete ophthalmic evaluation, including non-standardized Snellen VA testing; and SD-OCT at baseline and follow-up visits. A total of 23 patients who received IVO for VMT and/or MH were included for analysis. Patient age ranged from 53 years to 93 years with a mean of 74 years. The mean follow-up was 174 days (range: of 20 to 291 days). Vitreo-macular traction release at Day 30 after IVO was achieved in 11 of 23 patients (47.82 %), at an average of 14.54 days (range of 1 to 30 days) after treatment. The mean VA improved from 0.50 to 0.38.

At presentation, 8 patients had MH associated with VMT. Closure of the MH with ocriplasmin was achieved in 2 patients, and 6 patients underwent PPV for MH repair; 10 of 23 patients (43.47 %) presented with changes in the outer retina reflectivity on SD-OCT after IVO, 4 patients of this group experienced a decrease in VA. In 7 of these 10 patients (70 %), VMT release was documented on OCT by Day 30 post-injection compared with 4 of 13 patients (30.76 %) without outer retina changes post-IVO. Normalization of the outer retina reflectivity was achieved in all cases. The authors concluded that in this case series of VMT/MH patients treated with ocriplasmin, changes in the SD-OCT outer retina reflectivity were relatively common. Within weeks, the outer retinal reflectivity on SD-OCT improved, as did the VA. They stated that further studies to investigate the association between outer retina reflectivity changes with the use of IVO and long-term VA outcomes are needed.
Haller et al (2015) evaluated the effectiveness of a single IVO (125 μg) across relevant subpopulations of patients with symptomatic VMA/ VMT, including when associated with MH. This analysis entailed 2 multi-center, randomized, placebo-controlled, double-masked, 6-month studies with a total of 652 randomized patients (464 receiving ocriplasmin; 188 receiving placebo). Pre-specified subgroup analyses were conducted to evaluate the effects on the proportion of patients with non-surgical resolution of focal VMA at day 28, non-surgical FTMH closure at month 6, and categoric improvement in BCVA at month 6. Resolution of VMA at day 28 was achieved more often in younger patients (less than 65 years), eyes without epi-retinal membrane, eyes with FTMH, phakic eyes, and eyes with a focal VMA less than or equal to 1,500 μm. Eyes with FTMH width less than or equal to 250 μm were more likely to achieve non-surgical FTMH closure. Categoric greater than or equal to 2-line and greater than or equal to 3-line improvement in BCVA occurred more often in younger patients (less than 65 years) and in patients with a lower baseline BCVA (less than 65 letters). Treatment differences in favor of ocriplasmin were generally observed across each subgroup of subpopulations studied. The authors concluded that subgroup analyses confirmed the positive effect of ocriplasmin across relevant subpopulations.

Maier et al (2015) evaluated the resolution rate in patients with symptomatic VMT (less than or equal to 1,500 μm) with or without MHs (less than or equal to 400 μm) after therapy with IVO (Jetrea) injection in a clinical setting. Until now these researchers have prospectively examined 21 eyes of 21 consecutive patients with symptomatic VMT with or without MHs who underwent intra-vitreal operative injection of 0.1 ml ocriplasmin. The BCVA and SD-OCT ultrastructural parameters were measured before injection and again 1, 3 and 4 months after treatment. The numbers of resolved VMT and closed MHs were documented. Vitreo-macular traction was resolved in 15 out of 21 (71 %) eyes. Of the 5 eyes that initially presented with VMT with MHs, all showed resolution of VMT but only 2 of the MHs were closed. The average BCVA was 0.38 logMAR (± 0.23) at baseline and 0.43 logMAR (± 0.28), 0.38 logMAR (± 0.27) and 0.36 logMAR (± 0.24) 1, 3 and 4 months after injection, respectively. The average foveal thickness was 366.65 μm (± 114.53 μm) at baseline, reducing to 304.61 μm (± 100.91 μm), 308.00 μm (± 76.17 μm) and 277.50 μm (± 26.24 μm) after 1, 3 and 4 months, respectively. The authors concluded that in this ongoing study there was a high percentage of resolution of VMT (71 %) 1 month after intra-vitreal operative injection of ocriplasmin and closure of 2 out of 5 MHs. This was further associated with stabilization of VA and reduction of foveal thickness. They stated that further investigations are needed to document the effectiveness of the pharmacological vitreolysis in a clinical setting.

The prescribing information for Jetrea states that “Repeated administration of Jetrea in the same eye is not recommended”. The prescribing information also notes that a second intra-vitreal administration of ocriplasmin (28 days apart) in monkeys at doses of 75 ug/eye (41 mcg/ml vitreous) or 125 ug/eye (68 mcg/ml vitreous) was associated with lens subluxation in all
Ocriplasmin treated eyes. Sustained increases in IOP occurred in 2 animals with lens subluxation. Microscopic findings in the eye included vitreous liquefaction, degeneration/disruption of the hyaloideocapsular ligament (with loss of ciliary zonular fibers), lens degeneration, mononuclear cell infiltration of the vitreous, and vacuolation of the retinal inner nuclear cell layer. These doses are 1.4-fold and 2.3-fold the intended clinical concentration in the vitreous of 29 ug/ml, respectively.

Retinal Vein Occlusions

de Smet and colleagues (2016) noted that retinal vein occlusions (RVO) are a major cause of vision loss in people aged 50 years and older. Current therapeutic options limit the consequences of RVO but do not eliminate the cause. Cannulation of the involved vessel and removal of the clot may provide a more permanent solution with a less demanding follow-up. However, cannulation of smaller retinal veins remains challenging. These researchers examined the use of ocriplasmin to clear RVO, using a robotic micro-manipulator. Branch RVO were induced in a porcine model with rose bengal followed by 532 nm endo-laser to the superior venous branch of the optic nerve. The vein was cannulated proximal to the occlusion or beyond the first branching vessel from the obstruction. The vein was infused with a physiologic citric acid buffer solution (CAM) or CAM/ocriplasmin. The time of cannulation, number of attempts, and the ability to release the thrombus were recorded. Cannulation and infusion was possible in all the cases. The use of a micro-manipulator allowed for a consistent cannulation of the retinal vein and positional stability allowed the vein to remain cannulated for up to 20 mins. In none of the attempts (5/5) with CAM did the thrombus dissolve, despite repeat infusion/relaxation cycles. In 7/7 injections of CAM/ocriplasmin near to the point of obstruction, the clot started to dissolve within a few minutes of injection. An infusion, attempted beyond the first venous branch point proximal to the clot, was unsuccessful in 2/3 attempts. The authors concluded that ocriplasmin was effective in resolving RVO if injected close to the site of occlusion with the use of a micro-manipulator. These preliminary findings need to be further investigated in human subjects.

In an in-vivo, porcine retinal vein occlusion model, Willekens and associates (2017) examined the feasibility of robot-assisted retinal vein cannulation for the treatment of RVO. A standard 3-port pars plana vitrectomy was followed by laser-induced branch RVO. Consequently, a retinal vein cannulation with the help of a surgical robot and a microneedle was performed. Complete success was defined as a stable intravenous position of the needle tip confirmed by blood washout for at least 3 mins. Secondary outcomes were the occurrence of intra-operative complications and technical failures. Cannulation was successful in 15 of 18 eyes with a complete success rate (duration of infusion of more than 3 mins) of 73 % after exclusion of 2 eyes from analysis due to failure in establishing a blood clot. There were no technical failures regarding the robotic device. The intra-vessel injections of ocriplasmin in 2 of 2 eyes led to a clot
dissolution. In a subset of 5 eyes, a 2nd cannulation attempt at the border of the optic disc resulted in a stable intra-vessel position and infusion during 362 (± 138) seconds. The authors concluded that robot-assisted retinal vein cannulation with prolonged infusion time was technically feasible. They stated that human experiments are needed to analyze the clinical benefit of this new therapy.

Furthermore, an UpToDate review on “Retinal vein occlusion: Treatment” (Covert and Han, 2018) does not mention ocriplasmin as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”:*

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<th>Code Description</th>
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<td>67028</td>
<td>Intravitreal injection of a pharmacologic agent (separate procedure)</td>
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<tr>
<td>J7316</td>
<td>Injection, ocriplasmin, 0.125 mg</td>
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<tr>
<td>H43.821 - H43.829</td>
<td>Vitreomacular adhesion</td>
</tr>
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ICD-10 codes not covered for indications listed in the CPB (not all inclusive):
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<tr>
<td>E08.311, E08.3211, E08.3219, E08.3311, E08.3319, E08.3411, E08.3419, E08.3511, E08.3559</td>
<td>Diabetes mellitus due to underlying condition with ophthalmic complications</td>
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<tr>
<td>H34.8110, H34.8192</td>
<td>Central retinal vein occlusion</td>
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<td>H34.821 - H34.829</td>
<td>Venous engorgement</td>
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<td>H34.8310, H34.8392</td>
<td>Tributary (branch) retinal vein occlusion</td>
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<tr>
<td>H35.20, H35.23</td>
<td>Other non-diabetic proliferative retinopathy</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>H35.30</td>
<td>Unspecified macular degeneration</td>
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<tr>
<td>H35.341 - H34.349</td>
<td>Macular cyst, hole, or pseudohole</td>
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<tr>
<td>H43.10 - H43.13</td>
<td>Vitreous hemorrhage</td>
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<tr>
<td>I67.89</td>
<td>Other cerebrovascular disease</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


33. Covert DJ, Han DP. Retinal vein occlusion: Treatment. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2018.
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Aetna considers ocriplasmin (Jetrea) medically necessary for the treatment of symptomatic vitreo-macular adhesion (VMA). The 6 week duration noted above does not apply for the Pennsylvania Medical Assistance plan.