Subject: Jetrea (ocriplasmin) for Vitreomacular Adhesion	**Original Effective Date:** 6/13/2017
Policy Number: MCP-297	**Revision Date(s):**
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Disclaimer

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

Summary of Evidence/Position

This policy addresses Jetrea (ocriplasmin), proteolytic enzyme given by intravitreal injection for the treatment of symptomatic vitreomacular adhesion (VMA), when appropriate criteria are met.

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. VMA by itself is not hazardous; however the resulting vitreo-macular traction (VMT) can result in macular damage which may lead to loss or distortion of vision over time. (Arroyo 2016)

- Symptoms can be variable, but may include diminished visual acuity, distorted vision (metamorphopsia), and central field defect. Patients are usually observed until resolution or worsening, in which case vitrectomy is the standard treatment. Without treatment, most symptomatic retinal detachments progress to involve the entire retina and lead to loss of vision. (Arroyo 2016)
- Spontaneous release of VMA/VMT occurs in about 30% of cases over a period of 1 to 2 years, and observation is usually indicated because vitrectomy has risks and an almost certain occurrence of cataract in the years following vitrectomy (Jackson 2013).
- Vitrectomy, surgical procedure in which all or part of the vitreous gel from the eye is removed, was the only available intervention prior to the approval of ocriplasmin. (Tzu 2015)
- Ocriplasmin provides a pharmacologic therapeutic option to an otherwise surgically-treated condition.

Ocriplasmin (Jetrea) is a recombinant truncated form of human plasmin, a *proteolytic enzyme* that breaks down protein components at the vitreoretinal interface in the eye. Ocriplasmin works via proteolysis directed at laminin, fibronectin and collagen at the vitreous body/vitreoretinal interface. This results in dissolution of the protein-connector responsible for VMA. Ocriplasmin is injected into the affected eye as a single dose and can induce vitreous liquefaction and separation from the retina and is indicated for the treatment of symptomatic VMA.

The safety and efficacy of ocriplasmin was evaluated in two multicenter, randomized, double-blind, phase 3 trials. Study 006 and 007 comprise the **Microplasmin for Intravitreous Injection--Traction Release without Surgical Treatment (MIVI-TRUST)** clinical program.

- A total of 654 patients participated in MIVI-TRUST (464 received ocriplasmin and 188 received placebo).
- The study population included adults with focal VMA as seen on OCT and BCVA of 20/25 or less in their affected eye and 20/800 or more in the non-study eye.

In the two randomized, placebo-controlled trials of patients with VMA (n=652), significantly more patients achieved non-surgical resolution of adhesion and total posterior vitreous detachment after intravitreal injection of ocriplasmin compared with those receiving placebo. *Resolution of VMA at day 28 was achieved in 26.7% (n=123/464) of those receiving ocriplasmin compared with 10.1% (n=19/188) of those receiving placebo (odds ratio (OR), 3.28; 95% CI, 1.93 to 5.84; p less than 0.001) (Stalmans et al. 2012)*

Summary

Relevant outcomes include symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity.

Results of the randomized controlled trials demonstrate an improvement in the resolution of VMA/VMT at 28 days (26.7% vs 10.1% of patients) and a modest reduction in the proportion of patients undergoing vitrectomy (17.7% vs 26.6%).

Results of these trials also showed a modest increase in the proportion of patients who had clinically significant gains in visual acuity and visual function.

The RCTs did not find a higher rate of important complications; however, post-marketing surveillance has identified some previously unknown adverse effects with this novel enzymatic treatment.

The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Adverse Events A greater percentage of ocular adverse events were noted in the ocriplasmin vs. placebo groups (68.4 vs. 53.3%) in MIVI-TRUST. Most of these adverse events were mild and transient.

Ocriplasmin provides a pharmacologic therapeutic option to an otherwise surgically-treated condition. At this time, there is no published direct or indirect clinical trial data comparing ocriplasmin (Jetrea) to vitrectomy. It is unclear if it is more effective in the treatment of symptomatic VMA than the standard of care, pars plana vitrectomy. At 6 months, approximately 18% of patients treated with ocriplasmin underwent vitrectomy for persistent VMA. However, treatment with ocriplasmin is reported to led to successful resolution of VMA/VMT at 28 days occurred in 26.5% of ocriplasmin-treated patients in clinical trials (Stalmans et al. 2012); whereas, vitrectomy is successful in up to 90% of cases. (Arroyo 2016)

FDA Indications

Vitreomacular adhesion: Treatment of symptomatic vitreomacular adhesion

Orphan drug designation: Adjunct to surgery in cases of pediatric vitrectomy

Approved by the FDA: October 17, 2012

Available as: 0.125 mg (0.1 mL of diluted solution) via intravitreal injection to the affected eye once as a single dose

Black Box Warnings/REMS: None at the time of this writing

CLASSIFICATION: Ophthalmologic Agent; recombinant human plasmin

Coverage Criteria for Initial Authorization

Jetrea (ocriplasmin) for initial treatment of the *affected eye* may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ALL]

- ❒ Prescribed by board-certified ophthalmologists or retinal specialist experienced in the administration of intravitreal injections. Treatment and monitoring must be retained by the specialist.

2. Diagnosis/Indication [ALL]

Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

- ❒ Diagnosis symptomatic vitreomacular adhesion (VMA) or vitreomacular traction (VMT) documented by the following: [ALL]
  - ❍ Decreased visual acuity due to vitreomacular traction
  - ❍ Presence of symptoms due to vitreomacular traction in addition to decreased visual acuity. Symptoms may include, but are not limited to visual distortion, black spots, or floaters

Informational Note: VMA and VMT are sometimes used interchangeably; however the International Vitreomacular Traction Study Group has defined VMA as adhesion at the macula without detectable changes in retinal morphology and VMT as adhesion with retinal morphologic changes but without full-thickness defect. Both VMA and VMT can be focal or diffuse.

- ❒ Optical Coherence Tomography (OCT) confirms BOTH of the following: [BOTH]
  - ❍ Vitreous adhesion within 6-mm of the fovea (center of macula)
    **OCT demonstrates VMA to the macula within a 6-mm central retinal field*
  - ❍ Elevation of the posterior vitreous cortex (outer layer of the vitreous)
- ❒ Best-corrected visual acuity of <u>20/25 or less</u> in the affected eye (eye to be treated with ocriplasmin)
  - *The study population included adults with focal VMA as seen on OCT and BCVA of 20/25 or less in their affected eye and 20/800 or more in the non-study eye (MIVI-TRUST trial)*

MOLINA REVIEWER: Baseline labs (prior to treatment) noted in member's profile to review for reauthorization of treatment

3. Age/Gender/Restrictions [ALL]

- ❒ 18 years of age or older
  Safety and effectiveness in pediatric patients have not been established.

Ocriplasmin is not recommended for use in neonates, infants, children, or adolescents. When administered as an adjunct to vitrectomy to pediatric patients in a clinical study, there were no statistical or clinical differences between groups for the induction of total macular posterior vitreous detachment, any of the secondary endpoints, or adverse events.

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Member has not received previous treatment with Jetrea (ocriplasmin) for the eye requested

5. Contraindications*/Exclusions/Discontinuations

There are no contraindications listed in the manufacturer's labeling.

Authorization for Jetrea (ocriplasmin) will not be authorized if ANY of the following conditions apply [ANY]

- ❒ Hypersensitivity to dexamethasone or any component of the formulation
- ❒ Exclusions
  - ❍ Proliferative diabetic retinopathy

    The study population did not include patients with proliferative diabetic retinopathy or neovascular age-related macular degeneration and should not be used in these patients until further evidence supports its use.
  - ❍ Neovascular age-related macular degeneration
  - ❍ Retinal vascular occlusion
  - ❍ Aphakia
  - ❍ High myopia (more than -8 diopters)
  - ❍ Uncontrolled glaucoma
  - ❍ Macular hole >400 µm in diameter *NICE 2013*
  - ❍ Vitreous opacification
  - ❍ Lenticular or zonular instability
  - ❍ History of retinal detachment in either eye
  - ❍ Prior vitrectomy
  - ❍ Prior laser photocoagulation of the macula
  - ❍ Prior treatment with ocriplasmin
  - ❍ Treatment with ocular surgery, intravitreal injection, or retinal laser photocoagulation in the previous 3 months

- ❒ Precaution (not an Exclusion; however if noted in member's medical record, Peer-to-Peer or additional documentation from Prescriber may be requested)
  - ❍ Decreased visual acuity has been reported and may indicate progression of condition; monitoring recommended
  - ❍ Intraocular inflammation, infection, hemorrhage, and increased pressure
  - ❍ Lens subluxation has been reported with higher than recommended doses
  - ❍ Retinal detachment and retinal tear, mostly occurring during or after vitrectomy
  - ❍ Dyschromatopsia, in some cases with electroretinographic changes

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

Reauthorization /Continuation of Therapy

Jetrea (ocriplasmin) may **NOT** be reauthorized for re-treatment of the same affected eye.

Lifetime limit: ONE (1) dose per eye for lifetime.
The prescribing information for Jetrea states that "Repeated administration of Jetrea in the same eye is not recommended."

For treatment of bilateral VMA: At least seven (7) days must pass (to appropriately monitor for potential post-injection complications in the treated eye) before treatment of the contralateral eye may be administered.

All requests must meet Initial 'Recommendations/Coverage Criteria'

Administration, Quantity Limitations, and Authorization Period

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ONE]

Vitreomacular adhesion, Symptomatic

- ❒ Adults: 0.125 mg (0.1 mL of diluted solution) administered via intravitreal injection into the affected eye once as a single dose; repeat administration into the same eye is not recommended
  Each vial of ocriplasmin should only be used to provide a single injection for the treatment of a single eye.

  Pediatric: Use is not recommended in pediatric patients

- ❒ For treatment of bilateral VMA, a waiting period of at least seven (7) days is recommended before treatment of the contralateral eye to appropriately monitor for potential post-injection complications in the treated eye

2. Authorization Limit [ALL]

- ❒ Request is for ONE (1) of the following: [ONE]
  - ❍ A single intravitreal injection of ocriplasmin (Jetrea) for an eye with symptomatic VMA
  - ❍ Treatment of bilateral VMA: At least a 7 days has lapsed since treatment of the initial or contralateral eye as recommended
- ❒ **Lifetime limit: ONE (1) dose per eye** (one 0.2 ml vial)

3. Route of Administration [ALL]

- ❒ Jetrea (ocriplasmin) is considered a **provider-administered** by a qualified ophthalmologist experienced in intravitreal injections
  Ocriplasmin is administered via ophthalmic intravitreal injection only.
  NOTE: Repeated injections to the eyes will not be authorized due to lack of safety and efficacy data based on the FDA package insert.
- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

Coverage Exclusions

This policy only addresses the FDA approved indications of Jetrea (Ocriplasmin) when appropriate criteria are met.

All other uses of Jetrea (Ocriplasmin) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Jetrea (Ocriplasmin) is considered investigational and experimental for the following indications (not an all-inclusive list) as there is currently insufficient evidence to support the use of ocriplasmin for these indications:

- ❒ Age-related macular degeneration
- ❒ Catheter-related thrombosis
- ❒ Coronary artery thrombosis
- ❒ Diabetic retinopathy
- ❒ Foveal schisis (foveoschisis)
- ❒ Mobilization of hematopoietic progenitor cells
- ❒ Peripheral arterial occlusion
- ❒ 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 separation from the entire macula and optic disc)
- ❒ Stroke
- ❒ Surgical adjunct to vitrectomy
- ❒ Vitreous hemorrhage

Background/Summary

The primary evidence supporting ocriplasmin for symptomatic vitreomacular adhesion (VMA) is the published study by Stalmans et al for the MIVI-TRUST study group. The study presents pooled results of 2 identically designed, double-blind, placebo-controlled randomized trials. Results of these two studies are pooled and reported in a single publication (Stalmans et al., 2012).

The indication is based on two 6-month randomized, double-blind, placebo-controlled, phase III pivotal trials [TG-MV-006 (NCT00781859) and TG-MV-007 (NCT00798317)]. Results of these two studies are pooled and reported in a single publication (Stalmans et al., 2012).

- A single injection of ocriplasmin 0.125 mcg or placebo was given via intravitreal injection for the treatment of symptomatic VMA.
- A total of 652 eyes (n=652) (n=464 with ocriplasmin and n=188 with placebo) were randomized in these two studies and treated with a single injection of ocriplasmin or vehicle.
  - The study population included adults with focal VMA as seen on OCT and BCVA of 20/25 or less in their affected eye and 20/800 or more in the non-study eye.
- Subjects enrolled in the study met strict inclusion and exclusion criteria:
  - Subjects were not currently scheduled to have vitrectomy, but according to assessment by their physician, 84% were expected to need vitrectomy if their condition did not improve

Endpoints

- Primary endpoint: Resolution of VMA at day 28
- Secondary endpoints:
  - Posterior Vitreous Detachment (PVD)
  - Non-surgical closure of a macular hold at day 28
  - Avoidance of vitrectomy
  - Change in Best Corrected Visual Acuity (BCVA)

Results of randomized controlled trials (RCTs) demonstrate:

- MIVI-TRUST authors note that a limitation of their study was the inclusion of patients with baseline VA that is better than that of patients for whom vitrectomy would generally be recommended. Perhaps this is the reason that visual gains were considered modest.
- An improvement in the resolution of VMA/VMT at 28 days 28 occurred in 26.5% of ocriplasmin-treated patients and 10.1% of placebo-treated patients
- A modest increase in the proportion of patients who had clinically significant gains in visual acuity and visual function
- Other 28-day secondary end points, posterior vitreal detachment and closure of macular holes, also favored ocriplasmin.
- The RCTs did not find a higher rate of important complications; however, post-marketing surveillance has identified some previously unknown adverse effects with this novel enzymatic treatment.
    - Ocular adverse events were self-reported and 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 two groups (P=0.26)
    - The most common adverse events (2% to <5%) included: macular edema, increased intraocular pressure, anterior chamber cell, photophobia, vitreous detachment, ocular discomfort, iritis, cataract, dry eye, metamorphopsia, conjunctival hyperemia, and retinal degeneration.
- Results of these trials also showed a modest increase in the proportion of patients who had clinically significant gains in visual acuity and visual function.
- The RCTs did not find a higher rate of important complications; however, post-marketing surveillance has identified some previously unknown adverse effects with this novel enzymatic treatment.
- The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

  MIVI-TRUST supports a greater proportion of patients that received ocriplasmin achieved the primary endpoint of VMA resolution at day 28, compared to patients receiving placebo injection.
    - A greater proportion of patients treated with ocriplasmin achieved secondary endpoints of total posterior vitreous detachment and closure of macular hole at day 28. There was greater improvement in visual acuity with ocriplasmin at 6 months, but the improvement was considered to be modest.
    - MIVI-TRUST investigators noted that a limitation of their study was the inclusion of patients with baseline VA that is better than that of patients for whom vitrectomy would typically be recommended. Perhaps this is the reason that visual gains were considered modest.
    - The effects of ocriplasmin were noted in some, but not all of the patients received benefit from treatment. Ocriplasmin appeared to be more effective than placebo. It is unclear if it is more effective in the treatment of symptomatic VMA than the standard of care, pars plana vitrectomy.
    - At 6 months, approximately 18% of patients treated with ocriplasmin underwent vitrectomy for persistent VMA.
    - A greater percentage of ocular adverse events were noted in the ocriplasmin vs. placebo groups (68.4 vs. 53.3%) in MIVI-TRUST. Most of these adverse events were mild and transient.

  <u>Safety</u>
    - A greater percentage of ocular adverse events were noted in the ocriplasmin vs. placebo groups (68.4 vs. 53.3%) in MIVI-TRUST. Most of these adverse events were mild and transient.
    - The most common adverse events (5-20%) were: vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment and retinal edema.
    - Less common adverse events (2-5%) included macular edema, increased intraocular pressure, anterior chamber cell, photophobia, vitreous detachment, ocular discomfort, iritis, cataracts, dry eye, metamorphopsia, conjunctival hyperemia and retinal detachment.

  <u>Adverse Events</u>

  The American Society of Retina Specialists Therapeutic Surveillance Committee (2015) assessed adverse events from regulatory reports of 999 injections administered during clinical trials and voluntary reports of adverse events from 4387 doses administered post-marketing. This publication described some reports, in a small percentage of patients, of significant and permanent vision loss, electroretinogram changes, dyschromatopsia, retinal tear/detachment, lens subluxation, impaired pupillary reflex, loss or disruption of the ellipsoid zone, vascular

attenuation or vasoconstriction, and nyctalopia (night blindness). The rates of these adverse events cannot be determined with certainty due to the voluntary nature of reporting, raising the possibility of incomplete reporting.

Meta-Analysis

Chatziralli et al (2016) conducted a meta-analysis ocriplasmin for VMT.

- Results from 19 studies were pooled: RCT, cohort, case-control, or cross-sectional designs were included.
- No study quality (risk of bias) appraisal was performed.
- Factors predictive for VMT release were adhesion diameter, age less than 65 years, female, and lack of a phakic lens.
- The pooled rate of macular hole closure was 33% (95% CI, 326 to 39; I2=0%; 13 studies).
- Adverse event rates were summarized for 874 eyes including acute decrease in visual acuity (17.4%), subretinal fluid (8.8%), dyschromatopsia (0.9%), progression to macular hole (5.0%), retinal detachment/tear (1.8%), and afferent pupillary defect (0.1%).
- Except for decreased acute visual acuity, adverse event rates were considerably lower than those from the Shah et al (2016)* survey. While some factors were associated with response, implications are limited by the study-level nature of the meta-analysis.

  **Shah et al (2016) surveyed 2465 retinal physicians regarding ocriplasmin use and adverse events: 270 (11%) completed questionnaires (reporting on 1056 treated eyes). The most common adverse events reported included acute visual acuity decline (17.0%), retinal detachment or submacular fluid (10.2%), dyschromatopsia (9.1%), progression to macular hole (8.7%), retinal detachment (2.7%), retinal tear (2.0%), and afferent pupillary defect (1.8%). Reported adverse event rates were higher than those in clinical trial data (e.g., incidence of decline in visual acuity in trials was 7.7%). However, the survey-based estimates are likely to be impacted by the high rate of physician nonresponse.*

American Academy of Ophthalmology (AAO 2016)

The 2016 preferred practice pattern on idiopathic epiretinal membrane and vitreomacular traction offered the following recommendations:

- The treating physician should discuss the option of treating patients who have VMT with ocriplasmin and compare the treatment with observation, a gas bubble injected into the vitreous, or vitrectomy surgery. (Good quality, strong recommendation)
- The discussion should include the relevant risks versus benefits for each of these options. (Good quality, strong recommendation)

National Institute for Health and Care Excellence (NICE 2013)

NICE issued guidance on ocriplasmin for treating vitreomacular traction in 2013. Ocriplasmin is recommended as an option for treating VMT 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

Hayes

At the time of this writing, a Hayes assessment on "*Jetrea (Ocriplasmin Intravitreal Injection),*" is not available. A Prognosis Overview was published Oct 18, 2012 and has been archived since Feb 07, 2014.

Definitions

Aphakia: The absence of the lens of an eye, resulting from a congenital condition or as a result of trauma or surgery.

Central retina: A circular retinal field of approximately 6 mm around the fovea.

Glaucoma: A disease characterized by destruction of the nerve fiber layer of the optic disc.

Intravitreal or intravitreous: In the vitreous, the clear, jelly-like substance that fills the posterior segment of the eye.

Macula: A part of the retina responsible for reading vision.

Myopia: A condition in which the visual images come to a focus in front of the retina of the eye resulting especially in defective vision of distant objects.

Vitrectomy: The surgical removal of the vitreous.

Appendix

N/A

Coding Information: The codes listed in this clinical policy are for informational purposes only. listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive and Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT	Description
67028	Intravitreal injection of a pharmacologic agent

HCPCS	Description
J7316	Injection, ocriplasmin, 0.125 mg

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Package Insert, FDA, Drug Compendia

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Policy History	Approval
Policy Developed AMR Peer Review Network. Board certified in Ophthalmology. Date completed: 5/10/2017	MCPC 6/13/2017
Policy Reviewed 7/10/2018 (MCPC); Q4 2019 (P&T)	

**Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy revised/updated as appropriate.*