



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Ocriplasmin for Symptomatic Vitreomacular Adhesion (Jetrea)

Policy Number: 9.03.30
Origination: 10/2015

Last Review: 10/2018
Next Review: 10/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Jetrea (ocriplasmin) for Symptomatic Vitreomacular Adhesion when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

A single intravitreal injection of ocriplasmin may be considered **medically necessary** for treatment of an eye with symptomatic vitreomacular adhesion (VMA) or vitreomacular traction.

When Policy Topic is not covered

The use of intravitreal ocriplasmin is considered **investigational** in all other situations, including use of repeat injections of ocriplasmin.

Considerations

The precise patient indications for treatment are not certain. The eligibility criteria for the key randomized controlled trial included the following:

- Individual's age is equal to or greater than 18 years;
- Optical coherence tomography demonstrates all of the following:
 - There is vitreous adhesion within 6 mm of the fovea (center of macula); and
 - There is elevation of the posterior vitreous cortex (outer layer of the vitreous).
- Individual has best-corrected visual acuity of 20/25 or less in the eye to be treated with ocriplasmin
- Individual does not have any of the following:
 - proliferative diabetic retinopathy;
 - neovascular age-related macular degeneration;
 - retinal vascular occlusion;
 - aphakia;
 - high myopia (> -8 diopters);
 - uncontrolled glaucoma;
 - macular hole greater than 400 µm in diameter;
 - vitreous opacification;
 - lenticular or zonular instability;
 - history of retinal detachment in either eye;
 - prior vitrectomy in the affected eye;
 - prior laser photocoagulation of the macula in the affected eye;
 - prior treatment with ocular surgery, intravitreal injection or retinal laser photocoagulation in the previous 3 months.

Clinical input suggested that not all of the trial exclusion criteria should be absolute exclusions. However, there was not a consensus on the recommended exclusion criteria (see Supplementary Information section on clinical input received through physician specialty societies and academic medical centers).

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With vitreomacular adhesion/ vitreomacular traction 	Interventions of interest are: <ul style="list-style-type: none"> • Intravitreal injection of ocriplasmin 	Comparators of interest are: <ul style="list-style-type: none"> • Observation • Pars plana vitrectomy 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Change in disease status • Functional outcomes • Quality of life • Treatment-related morbidity

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 is injected into the affected eye (intravitreal) as a single dose and can induce vitreous liquefaction and separation from the retina. Its proposed use is for the treatment of symptomatic vitreomacular adhesion/vitreomacular traction (VMA/VMT).

The evidence for intravitreal injection of ocriplasmin in patients with VMA/VMT includes 2 large, double-blind, placebo-controlled, clinical trials and other supporting studies. Relevant outcomes include symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of randomized controlled trials (RCTs) demonstrate an improvement in the resolution of VMA/VMT at 28 days (26.5% 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, postmarketing 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.

Clinical input suggested that not all of the trial exclusion criteria should be absolute exclusions. However, there was no consensus on which exclusion criteria should be removed.

Background

The vitreous is a gel-like fluid within the eye that adheres completely to the surface of the retina. The consistency of the vitreous and its adhesion to the retina are maintained by several proteins including collagen, laminin, and fibronectin. With aging, the proteins in the vitreous break down, resulting in liquefaction of the vitreous and eventual separation of the vitreous from the retina, a process called posterior vitreous detachment (PVD).

The process of vitreous detachment usually proceeds without incident, but sometimes the separation is not complete. The adhesion usually remains at sites where the bonds between the vitreous and retina are the strongest. In some cases, the adhesion can cause visual symptoms. The traction caused by the adherent vitreous can cause deformation of the retina, edema, and full-thickness macular holes (FTMH). Although the terms are sometimes used synonymously, the International Vitreomacular Traction Study Group has defined vitreomacular adhesion (VMA) as adhesion at the macula without detectable changes in retinal morphology and vitreomacular traction (VMT) as adhesion with retinal morphologic changes but without full-thickness defect.¹ Both VMA and VMT can be focal or diffuse.

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. 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.^{2,3}

Ocriplasmin is a recombinant product that is a shortened form of the protease plasmin. Early studies of ocriplasmin were conducted in patients who were scheduled to have vitrectomy and established doses that showed some effect in inducing PVD and the temporal course of the effect. Studies by Benz et al,

de Smet et al, and Stalmans et al led to the design and conduct of the pivotal clinical trials described in the Rationale section of this evidence review.⁴⁻⁶

Rationale

The evidence review was originally based on a TEC Assessment,⁷ which concluded that ocriplasmin is associated with higher rates of resolution of vitreomacular adhesions, closure of macular holes, lower rates of vitrectomy and improvement in some measures of visual acuity, without increases in major adverse events, when compared with watchful waiting with vitrectomy as indicated. This demonstrates improvement in health outcomes.

The principal evidence supporting ocriplasmin for symptomatic vitreomacular adhesion (VMA) is the published study by Stalmans et al for the MIVI-TRUST study group.⁸ The study presents pooled results of 2 identically designed, double-blind, placebo-controlled randomized trials. Patients enrolled in the study met strict inclusion and exclusion criteria. They 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. Overall, 652 eyes were treated; 464 with ocriplasmin and 188 with placebo. The principal end point of the study, resolution of VMA at 28 days, occurred in 26.5% of ocriplasmin-treated patients and 10.1% of placebo-treated patients. Other 28-day secondary end points—posterior vitreal detachment and closure of macular holes—also favored ocriplasmin.

Secondary outcomes measured beyond 28 days were also better in ocriplasmin-treated eyes. By 6 months, 17.7% of ocriplasmin-treated subjects had undergone vitrectomy versus 26.6% of placebo-treated subjects. Visual improvement results varied depending on how the data were analyzed, but generally favored ocriplasmin. Measured as categorical improvement of 3 or more lines on the Early Treatment of Diabetic Retinopathy chart, ocriplasmin-treated subjects had higher success rates than placebo-treated subjects. Absolute gains in both groups were modest, particularly in the analysis where improvement was only counted in those who did not undergo vitrectomy (9.7% and 3.7%, respectively). A higher proportion of patients in the ocriplasmin group had a clinically meaningful (≥ 5 point) improvement on 25-item National Eye Institute Visual Function Questionnaire scores (36.0% vs 27.2%, $p=0.03$), and fewer ocriplasmin-treated patients had a clinically meaningful worsening in their visual function compared with the placebo group (15.0% vs 24.3%, $p=0.005$).⁹ Serious adverse events (SAEs) in ocriplasmin-injected eyes were not significantly different from placebo-injected eyes (7.7% ocriplasmin, 10.7% placebo).¹⁰ The most common adverse effects reported in patients treated with ocriplasmin include eye floaters; bleeding of the conjunctiva, eye pain; flashes of light (photopsia); blurred vision; vision loss; retinal edema (swelling); and macular edema.

A phase 2 randomized, sham-controlled trial in 100 patients with age-related macular degeneration (AMD) was primarily intended to evaluate adverse effects, but also reported on efficacy results.¹¹ Adverse events were higher in the ocriplasmin group, and SAEs in the study eye were observed in 10.7% of ocriplasmin-injected eyes compared with 0% sham-treated eyes. The efficacy in releasing VMAs was numerically similar to the MIVI-TRUST trial, but the difference was not statistically significant (24.3% vs 12.0%, $p=0.26$). Visual acuity was similar for the 2 groups.

A 2015 report for the American Society of Retina Specialists Therapeutic Surveillance Committee assessed adverse events from regulatory reports of 999 injections administered during clinical trials and voluntary reports of adverse events from 4387 doses administered postmarketing.¹² 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02035748 ^a	Assessment of Anatomical and Functional Outcomes in Patients Treated With Ocriplasmin for Vitreomacular/Symptomatic Vitreomacular Adhesion (VMT/sVMA)	400	Sep 2015
NCT02079883 ^a	Ocriplasmin Research to Better Inform Treatment (ORBIT)	1500	Apr 2016
NCT02322229 ^a	Assessment of Anatomical and Functional Outcomes in Subjects Treated With Ocriplasmin for Vitreomacular Traction/Symptomatic Vitreomacular Adhesion (VMT/sVMA)	400	Sep 2016

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for intravitreal injection of ocriplasmin in patients with vitreomacular adhesion/vitreomacular traction (VMA/VMT) includes 2 large, double-blind, placebo-controlled, clinical trials and other supporting studies. Relevant outcomes include symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of randomized controlled trials (RCTs) demonstrate an improvement in the resolution of VMA/VMT at 28 days (26.5% 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, postmarketing 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.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 1 physician specialty society and 1 academic medical center while this policy was under review. Clinical input suggested that not all of the trial exclusion criteria should be absolute exclusions. However, there was not a consensus on which exclusion criteria should be removed. Individual reviewers suggested removing the following exclusion criteria: macular hole greater than 400 µm; proliferative diabetic retinopathy; vitreous opacification; aphakia; high myopia; neovascular age-related macular degeneration; history of retinal detachment; and uncontrolled glaucoma. In addition, it was suggested that ocriplasmin may be beneficial for the treatment of macular holes and vitreous hemorrhage.

Practice Guidelines and Position Statements

In 2013, the National Institute for Health and Care Excellence (NICE) issued guidance on ocriplasmin for treating VMT.¹³ NICE recommends ocriplasmin 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Billing Coding/Physician Documentation Information

67028 Intravitreal injection of a pharmacologic agent (separate procedure)

J7316 Injection, ocriclasmin, 0.125 mg

ICD-10 H43.82 Vitreomacular Adhesion

ICD-10 H43.821 Vitreomacular adhesion, right eye

ICD-10 H43.822 Vitreomacular adhesion, left eye

ICD-10 H43.823 Vitreomacular adhesion, bilateral

ICD-10 H43.829 Vitreomacular adhesion, unspecified eye

This is a medical benefit

Additional Policy Key Words

9.03.30; Jetrea

Policy Implementation/Update Information

10/2015	New Policy. Ocriplasmin may be considered medically necessary for treatment of symptomatic vitreomacular adhesions.
10/2016	Annual review; no changes to policy statement
10/2017	Annual review; no changes to policy statement
10/2018	Annual review; no changes made

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