

PRODUCT MONOGRAPH

Pr **JETREA**[®]

ocriplasmin solution for intravitreal injection

2.5 mg/mL

Professed Standard

Ophthalmological

Sponsor:

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Pr **JETREA**[®]

(ocriplasmin)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravitreal	Sterile solution for intravitreal injection after dilution / 2.5 mg/mL	Not applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

Ocriplasmin is a recombinant truncated form of human plasmin obtained from microplasminogen produced in a *Pichia pastoris* expression system by recombinant DNA technology with a molecular weight of 27.2 kD.

INDICATIONS AND CLINICAL USE

JETREA[®] (ocriplasmin) solution for intravitreal injection is indicated for:

- the treatment of symptomatic vitreomacular adhesion (VMA).

Geriatrics (≥ 65 years of age):

The elderly population has been studied in clinical studies. No dose adjustment is required.

Pediatrics (< 18 years of age):

The safety and efficacy of JETREA in the pediatric population with symptomatic VMA have not been established. No data are available.

CONTRAINDICATIONS

- Hypersensitivity to ocriplasmin or to any of the excipients in JETREA (see DOSAGE FORMS, COMPOSITION AND PACKAGING)
- Active or suspected ocular or periocular infections

WARNINGS AND PRECAUTIONS

General

JETREA (ocriplasmin) is administered by intravitreal injection only.

Ophthalmologic

Intravitreal injections have been associated with intraocular inflammation/infection, intraocular hemorrhage and increased intraocular pressure (IOP). Proper aseptic injection techniques must always be used. Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available (see DOSAGE AND ADMINISTRATION).

Following intravitreal injection, patients should be instructed to report symptoms suggestive of endophthalmitis or retinal detachment (e.g. eye pain, redness of the eye, photophobia, blurred or decreased vision) without delay (see CONSUMER INFORMATION).

The safety and efficacy of JETREA administered to both eyes concurrently has not been studied and administration to both eyes concurrently is therefore not recommended.

Repeated administration of JETREA in the same eye has not been adequately studied and is therefore not recommended.

JETREA has not been studied in patients with large diameter macular holes (> 400 µm), high myopia (> 8 dioptre spherical correction or axial length > 28 mm), aphakia, history of retinal detachment, lens zonule instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration (AMD) and vitreous hemorrhage. Treatment is not recommended in such patients.

There is limited experience in patients with non proliferative diabetic retinopathy or history of uveitis or significant eye trauma. Caution should be exercised when treating such patients.

There is currently no clinical data on concomitant use of JETREA with VEGF-inhibitors.

The potential for lens subluxation cannot be ruled out, but the risk in adults is considered to be low (see ADVERSE REACTIONS and TOXICOLOGY).

Due to a potential increase in tractional forces, the occurrence of new or enlarged macular holes cannot be ruled out (see ADVERSE REACTIONS).

There is a risk for a significant, but transient loss of visual acuity during the first week after the injection due to the release of vitreomacular traction (see ADVERSE REACTIONS). Patients should be monitored appropriately.

The effect of JETREA (particularly in inducing resolution of vitreomacular adhesion (VMA) or causing total posterior vitreous detachment (PVD)) is reduced in subjects with an epiretinal membrane or a diameter of VMA > 1500 µm (see CLINICAL TRIALS).

Dyschromatopsia was reported following intravitreal injection of JETREA (see ADVERSE REACTIONS).

Ophthalmological examinations may be abnormal following the administration of JETREA. These include optical coherence tomography (OCT), ophthalmoscopy (foveal reflex), colour vision test (Roth 28-hue) and full-field ERG (see ADVERSE REACTIONS).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity for this product has not been evaluated.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with ocriplasmin. There are no adequate and well-controlled studies of ocriplasmin in pregnant women. It is not known whether ocriplasmin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The systemic exposure to ocriplasmin is expected to be very low after intravitreal injection of a single 0.125 mg dose. Assuming 100% systemic absorption (and a plasma volume of 2 700 mL), the estimated plasma concentration is 46 ng/mL. JETREA should be given to a pregnant woman only if clearly needed.

Nursing Women: It is not known whether ocriplasmin is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when JETREA is administered to a nursing woman.

Pediatrics (< 18 years of age): The safety and efficacy of JETREA in pediatric patients has not been established.

Geriatrics (≥ 65 years of age): The elderly population has been studied in clinical studies. No dose adjustment is required.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Over 800 patients have been treated with an intravitreal injection of ocriplasmin with over 570 patients treated with the recommended dose of 0.125 mg (JETREA).

Most adverse drug reactions (ADRs) were ocular, which is consistent with the intravitreal route of administration, rapid inactivation and limited systemic bioavailability; and most occurred within 0-7 days post injection. The most common ADRs were consistent with pharmacologic vitreolysis such as vitreous floaters, photopsia, or were due to inflammation/irritation resulting from either the injection procedure and/or the drug. These visual symptoms were also perceived in the contralateral eye or bilaterally. The majority of ADRs were non-serious, mild to moderate in intensity and resolved.

The most notable safety findings were those related to visual function changes (i.e. visual impairment, dyschromatopsia and/or electroretinogram changes). Most of these findings were non-serious, of mild intensity and resolved.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Approximately 800 patients have been treated with an intravitreal injection of ocriplasmin. Of these, 465 patients received an intravitreal injection of ocriplasmin at the recommended dose of 0.125 mg (187 patients received placebo) in the 2 placebo-controlled studies (TG-MV-006 and TG-MV-007).

The pivotal studies, TG-MV-006 and TG-MV-007, were both multicentre, randomized, placebo-controlled, double-masked, 6-month studies that investigated the safety and efficacy of a single intravitreal injection of JETREA 0.125 mg in patients with symptomatic vitreomacular adhesion. The 2 trials were identical in design (except for allocation ratio of 2:1 in TG-MV-006 and 3:1 in TG-MV-007) and conduct (except for geography: TG-MV-006 conducted in the USA and TG-MV-007 conducted in the EU and USA). A total of 652 patients were randomized (188, placebo; 464, JETREA); of these, 93.1% patients completed the studies. A total of 16 (8.5%) patients in the placebo group and 29 (6.3%) patients in the ocriplasmin group were discontinued from the studies. The mean age was 71.7 years (median 72 years; range 18 to 97 years).

Table 1 lists the adverse drug reactions (i.e. adverse events where there was a reasonable possibility that they were treatment related) which occurred at $\geq 1\%$ in the two pivotal studies. Vitreous floaters, eye pain and photopsia were the most common adverse reactions. Most adverse reactions were of mild or moderate intensity, had an onset 0-7 days post-injection and resolved within 2-3 weeks.

Serious adverse events (SAEs) were reported for 62 (13.3%) and 24 (12.8%) patients in the JETREA and placebo groups, respectively in the two pivotal trials. The incidence of drug-related SAEs was 3.2% in each treatment group. For SAEs regardless of causality, the majority were ocular events and these occurred in the study eye. The SAEs reported most frequently for JETREA were macular hole (including progression of macular hole [5.2%]), vitreous adhesions (i.e. vitreomacular traction progression [1.1%]) and for placebo, macular hole (8.6%) and retinal detachment (1.6%).

Adverse events that led to withdrawal were 4 (0.9%) in the ocriplasmin group and 2 (1.1%) in the placebo group for the pivotal trials.

Visual acuity reduced

In the pivotal studies (TG-MV-006 and TG-MV-007), 7.7% of JETREA patients and 1.6% of placebo patients had acute ≥ 2 -line (≥ 10 ETDRS letters) loss in best-corrected visual acuity (BCVA) during the first week after injection with no alternative explanation for the change. The visual acuity decrease had resolved by the end of the studies for the majority of JETREA patients (80.6%) but there were some patients who had not recovered despite vitrectomy. The median time to resolution was 22 days. At the end of the studies (Month 6), 36/464 (7.8%) patients in the JETREA group and 11/188 (5.9%) patients in the placebo group experienced a ≥ 2 -line loss in BCVA. See DOSAGE AND ADMINISTRATION for monitoring recommendations.

In study TG-MV-014, 2.8% of JETREA patients and 1.4% of sham patients had acute ≥ 2 -line loss in BCVA during the first week after injection, non/pre-vitrectomy. These events were not resolved by End of Study (EOS).

Intraocular inflammation, intraocular hemorrhage, increased intraocular pressure

Intravitreal injections are associated with intraocular inflammation / infection, intraocular hemorrhage and increased intraocular pressure (IOP). In the pivotal trials, the overall incidence of AEs in the intraocular inflammation category was higher in the JETREA group compared to placebo (7.1% vs 3.7%). None of the events considered drug-related were serious and most were mild in severity. Intraocular hemorrhage occurred in 2.4% vs 3.7% of patients injected with JETREA vs placebo, respectively. Increased intraocular pressure occurred in 4.1% vs 5.3% of patients injected with JETREA vs placebo, respectively. These rates are regardless of causality.

Retinal breaks (tears and detachment)

In the pivotal trials (TG-MV-006 and TG-MV-007), the incidence of retinal breaks (tears and detachment) were reported in 1.9% of patients injected with JETREA vs 4.3% injected with placebo. Most of these events occurred during or after vitrectomy in both groups. The incidence

of retinal tears and retinal detachment that occurred previtrectomy was 0.2% and 0.4%, respectively in the JETREA group, similar to what was observed in the placebo group (0.5% and 0%, respectively). These rates are regardless of causality.

Chromatopsia (including dyschromatopsia and colour vision test abnormal)

Colour vision alterations (including yellowish vision and abnormal Roth 28-hue colour vision test) were very commonly reported adverse events in study TG-MV-014; chromatopsia was reported by 59/146 (40.4%) subjects with 111 events in the ocriplasmin group and by 15/74 (20.3%) subjects with 21 events in the sham group. The median time to resolution of the first episode of chromatopsia was 78 days in the ocriplasmin group and 85 days in the sham group.

Retinogram abnormal

Electroretinographic (ERG) changes (a- and b-wave amplitude decrease) were reported in 11/976 (1.1%) patients injected with JETREA; in 9 of the 11 cases visual impairment and chromatopsia were also reported.

In 6 of the 11 cases, the ERG changes had resolved at the time of the last follow-up. The median time to resolution was 6 months. ERG changes were not predictive of negative outcomes in terms of visual acuity. ERG changes were reported in 5/247 (2.0%) placebo/control patients.

Macular Hole

In the pivotal studies (TG-MV-006 and TG-MV-007), events of macular hole (including both progression and new onset) were reported for 6.7% of all patients injected with JETREA vs 9.6% injected with placebo at Month 6.

In study TG-MV-014, events of macular hole (including both progression and new onset) were reported in 15.8% JETREA vs. 13.5% sham recipients at Month 24.

Early progression rates of full-thickness macular hole (until Day 7 post-injection) at RPE (retinal pigment epithelium) level were higher in the JETREA treated patients compared to sham or placebo. Progression rates after Month 6, however, were higher in sham or placebo than in those treated with JETREA. Any persistence or progression of macular hole should be treated according to usual practice.

Lens subluxation

One case of lens subluxation was reported in a patient who received an intravitreal injection of 0.175 mg (1.4 times higher than the recommended dose). Also refer to the Toxicology section for related animal data. Based on the proteolytic activity of JETREA and preclinical and clinical findings, the potential for lens subluxation cannot be ruled out.

Optical coherence tomography abnormal

In study TG-MV-014, incomplete Inner Segment/Outer Segment (IS/OS) band, also referred to as Ellipsoid Zone, in the central area was very common at baseline (65.8% in the JETREA group and 62.2% in the sham group). However, after treatment, a higher proportion of patients in the JETREA group had a change from an intact IS/OS band at baseline to an incomplete IS/OS band

in the central area at a later time point compared with the sham group (7.7% and 2.8%, respectively at Day 28).

Table 1 Adverse Drug Reactions \geq 1% for JETREA Pivotal Trials (TG-MV-006 and -007)

System Organ Class Preferred Term Category	Placebo, n=187 N (%)	JETREA 125 μg, n=465 N (%)
Eye Disorders		
Vitreous floaters	14 (7.5%)	78 (16.8%)
Eye pain	11 (5.9%)	61 (13.1%)
Photopsia	5 (2.7%)	55 (11.8%)
Vision blurred	6 (3.2%)	39 (8.4%)
Visual acuity reduced	8 (4.3%)	29 (6.2%)
Visual impairment	2 (1.1%)	25 (5.4%)
Retinal oedema	2 (1.1%)	25 (5.4%)
Macular oedema†	3 (1.6%)	19 (4.1%)
Anterior chamber cell	5 (2.7%)	17 (3.7%)
Photophobia	0 (0.0%)	17 (3.7%)
Ocular discomfort	2 (1.1%)	13 (2.8%)
Vitreous detachment	2 (1.1%)	12 (2.6%)
Iritis	0 (0.0%)	12 (2.6%)
Dry eye	2 (1.1%)	11 (2.4%)
Metamorphopsia	1 (0.5%)	10 (2.2%)
Retinal degeneration	1 (0.5%)	8 (1.7%)
Eyelid oedema	1 (0.5%)	7 (1.5%)
Retinal pigment epitheliopathy	0 (0.0%)	7 (1.5%)
Macular degeneration	1 (0.5%)	6 (1.3%)
Miosis	0 (0.0%)	5 (1.1%)
Scotoma	0 (0.0%)	5 (1.1%)
Corneal abrasion	0 (0.0%)	5 (1.1%)

†including cystoid macular oedema

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Pivotal Trials TG-MV-006 and -007

Eye disorders: Ocular hyperaemia (0.9%), Conjunctival irritation (0.9%), Diplopia (0.9%), Visual field defect (0.6%), Pupils unequal (0.6%)

Post-Market Adverse Drug Reactions

Ocular adverse drug reaction identified during post-marketing experience include the following:
Pupillary reflex impaired with an incidence rate of \geq 0.1% (uncommon).
Night blindness with an incidence rate of \geq 0.1% (uncommon).

In a randomized, double-masked, sham-controlled, 24-month study in 220 patients with vitreomacular traction/vitreomacular adhesion (JETREA 146, sham 74), the following additional notable adverse event was observed: lacrimation increase with an incidence rate of $\geq 1\%$ and $< 10\%$ (common).

DRUG INTERACTIONS

Overview

No formal interaction studies have been performed for JETREA (ocriplasmin).

Ocriplasmin is a proteolytic enzyme with serine protease activity which could be present in the eye for several days after intravitreal injection (see Clinical Pharmacology). Administration in close temporal association with other medicinal products in the same eye may affect the activity of both medicinal products and is therefore not recommended. No systemic interactions are anticipated.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Must be diluted with sterile preservative-free 0.9% w/v saline before use. For single-use ophthalmic intravitreal injection only. JETREA (ocriplasmin) must only be administered by a qualified health professional.

Recommended Dose and Dosage Adjustment

The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose.

No special dosage modification is required for any of the populations that have been studied (e.g. gender, elderly).

Administration

Preparation for Administration:

To prepare JETREA for intravitreal injection, adhere to the following instructions:

1. Remove the vial (2.5 mg/mL corresponding to 0.5 mg ocriplasmin) from the freezer and allow to thaw at room temperature (approximately 2 minutes).
2. Once completely thawed, remove the protective polypropylene flip-off cap from the vial.
3. The top of the vial should be disinfected with an alcohol wipe.
4. Using aseptic technique, dilute by adding 0.2 mL of sodium chloride 9 mg/mL (0.9%) solution for injection (sterile, preservative-free, non-buffered) into the JETREA vial (see Figure 1) and gently swirl the vial until the solutions are mixed (see Figure 2). Note: Do NOT shake. The diluent should be withdrawn from an unopened container which should be used only once. The remaining sodium chloride 9 mg/mL (0.9%) solution for injection should be discarded.

Figure 1



Figure 2



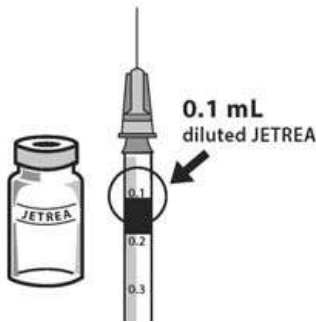
5. Visually inspect the vial for particulate matter. Only a clear, colourless solution without visible particles should be used.
6. Using aseptic technique, withdraw all of the diluted solution using an appropriate sterile needle (slightly tilt the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents (see Figure 3). Do not use this needle for the intravitreal injection.

Figure 3



7. Replace the needle with an appropriate sterile needle, carefully expel the air bubbles and excess drug from the syringe and adjust the dose to the 0.1 mL mark on the syringe (corresponding to 0.125 mg ocriplasmin) (see Figure 4).

Figure 4



8. THE SOLUTION SHOULD BE USED IMMEDIATELY AS IT CONTAINS NO PRESERVATIVES.
9. Discard the vial and any unused portion of the diluted solution after single use.

Administration:

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad spectrum microbiocide should be administered according to standard medical practice.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus aiming towards the center of the vitreous cavity, avoiding the horizontal meridian. The injection volume of 0.1 mL is then delivered into the midvitreous.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report symptoms suggestive of endophthalmitis or retinal detachment (e.g. eye pain, redness of the eye, photophobia, blurred or decreased vision) without delay (see CONSUMER INFORMATION).

Each vial 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 is administered to the other eye. However, treatment with JETREA 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 in the same eye is not recommended.

After injection, any unused product must be discarded.

OVERDOSAGE

The clinical data on the effects of JETREA (ocriplasmin) overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) has been reported to be associated with inflammation and a decrease in visual acuity.

If an overdose occurs, close monitoring is recommended. If an adverse reaction occurs, it should be treated according to standard medical practice.

EFFECTS ON ABILITY TO DRIVE VEHICLES AND OPERATE MACHINERY

The intravitreal injection of ocriplasmin may be followed by temporary visual disturbances. In these cases, patients should not drive or use machines until the visual disturbances have resolved.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 abnormal vitreomacular adhesion (VMA).

Pharmacodynamics

Ex vivo pharmacodynamics in human donor eyes was performed. Eyes were injected with 62.5, 125 or 188 µg ocriplasmin (n=4, 7 and 2 eyes respectively) to demonstrate the efficacy of ocriplasmin in inducing posterior vitreous detachment (PVD) and evaluate the human retina after treatment. Intravitreal injection of 125 and 188 µg ocriplasmin resulted in complete PVD in all 9 eyes. Complete vitreoretinal separation was induced in a dose- and time dependent fashion without morphologic damage to the retina. An intravitreal injection of 125 µg ocriplasmin was sufficient to induce complete PVD with bare internal limiting membrane within 30 minutes (Gandorfer et al., 2004).

Pharmacokinetics

The intravitreal pharmacokinetics of ocriplasmin were determined in a clinical study in patients scheduled for vitrectomy where 0.125 mg ocriplasmin (corresponding to an average concentration of 29 µg ocriplasmin per mL vitreous volume [approximately 4.3 mL/eye]) was administered as a single intravitreal dose at different time points prior to vitrectomy. The mean ocriplasmin activity levels decreased with time from injection to time of sampling as illustrated in Table 2, according to a second-order kinetic process. At 24 hours post injection the levels in the vitreous were below 3% of the theoretical concentration reached immediately after injection.

Because of the small dose administered (0.125 mg), detectable levels of ocriplasmin in systemic circulation are not expected after intravitreal injection.

Table 2: Mean Ocriplasmin Activity Levels in Vitreous Samples After Injection of 0.125 mg JETREA

Time Post-Injection (subjects)	5-30 min (n=8)	31-60 min (n=8)	2-4 hours (n=8)	24 hours (n=4)	7 days (n=4)
Mean ± SD Ocriplasmin levels (µg/mL)	12 ± 7.6	8.1 ± 5.2	2.6 ± 1.6	0.5 ± 0.3 ^a	<0.27 ^b

^a 2 subjects below lower limit of detection, other 2 subjects at 0.88 and 0.57 µg/mL

^b Lower limit of detection

Ocriplasmin enters the endogenous protein catabolism pathway through which it is rapidly inactivated via its interactions with protease inhibitor α2-antiplasmin or α2-macroglobulin.

The inactive ocriplasmin/α2 antiplasmin complex is cleared from the circulation with a half-life (t_{1/2}) of several hours.

No human metabolism or excretion studies have been conducted with ocriplasmin.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of ocriplasmin in the pediatric population has not been established. No data are available.

Hepatic Insufficiency: No formal studies have been conducted with JETREA in patients with hepatic impairment. No dose adjustment or special considerations are anticipated for patients with hepatic impairment.

Renal Insufficiency: No formal studies have been conducted with JETREA in patients with renal impairment. No dose adjustment or special considerations are anticipated for patients with renal impairment.

STORAGE AND STABILITY

Store in a freezer at -20°C±5°C. Protect the vials from light by storing in the original carton until time of use.

SPECIAL HANDLING INSTRUCTIONS

JETREA (ocriplasmin) is preservative-free and for single use only, immediately following dilution. The vial and any unused portion of the diluted solution should be discarded after single use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JETREA (ocriplasmin) is a sterile, clear, colourless solution with no preservatives in a single-use 2 mL glass vial with a latex-free rubber stopper. The pH of the solution is 3.1.

Medicinal ingredient: each vial contains 0.5 mg ocriplasmin in 0.2 mL solution for intravitreal injection after dilution.

Nonmedicinal ingredients: citric acid, mannitol, sodium hydroxide (for pH adjustment) and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ocriplasmin

Chemical name: microplasmin or recombinant truncated human plasmin

Molecular formula and molecular mass: 27237 Daltons

Structural formula:

Ocriplasmin is a protein of 249 amino acid residues. The protein consists of 2 peptide chains. The first peptide is 19 amino acid residues long. The second is 230 amino acid residues long. The peptides are linked together by 2 disulfide bonds between C6:C124 and C16:C24 residues according to the residue numbering presented in Figure 1. Four other disulfide bonds link the cysteine residues in the second peptide as C46:C62, C138:C205, C168:C184 and C195:C223. Ocriplasmin does not contain O- or N-linked glycosylation. The ocriplasmin amino acid sequence is presented in Figure 5.

Figure 5: Schematic Amino Acid Sequence of Ocriplasmin Written From N-Terminus to the C-Terminus. All 6 Disulfide Bridges are Shown (Full Lines). The 2 Peptides are Separated by (/)

```
APSFDCGKPKQVEPKKCPGR/VVGGCVAHPHSWPWQVSLRTR 40
FGMHFCGGTLISPEWVLTAAHCLEKSPRPSSYKVI LGAHQ 80
EVNLEPHVQEI EVSRLFLEPTRKDIAL LKLS SPAVITDKV 120
I PA CLPSENYV VADRTECFITGWGETQGTFGAGLLKEAQL 160
PVI ENKVCNRYEFLNGRVQSTELCAGHLAGGTDSQ QGDSG 200
GPLVCFEKDKYILQGVTSWGLGCARP NKPGVYVVRVSRFVT 240
WIEGVMRNN 249
```

Product Characteristics

Recombinant human ocriplasmin is produced in the transformed yeast *Pichia pastoris* by standard fermentation technology and purified using standard biotechnology purification procedures. Fermentation of *P. pastoris* results in the secretion of microplasminogen which is purified and converted to ocriplasmin using an activation chromatography step. The active ocriplasmin is then further purified and formulated.

CLINICAL TRIALS

Study demographics and trial design

The efficacy of JETREA (ocriplasmin) was demonstrated in two multicenter, randomized, double masked, placebo controlled, 6 month studies in patients with symptomatic vitreomacular adhesion (VMA). A total of 652 patients (JETREA 464, placebo 188) were randomized in these 2 studies (TG-MV-006 and TG-MV-007). Randomization was 2:1 (JETREA:placebo) in study TG-MV-006 and 3:1 in study TG-MV-007 (Stalmans et al., 2012).

In both studies the majority of the patients were female (63.5% in TG-MV-006 and 68.1% in TG-MV-007). Mean age was 71.3 years (overall range: 18 to 96 years) in TG-MV-006 and 72.0 years (overall range: 23 to 97 years) in TG-MV-007. The majority of the patients were white (89.6% in TG-MV-006 and 95.1% in TG-MV-007). Mean BCVA at baseline was 64.8 letters in TG-MV-006 and 63.8 letters in TG-MV-007. The proportion of patients with full thickness macular hole (FTMH) at baseline was 27.3% in study TG-MV-006 and 19.6% in TG-MV-007. In study TG-MV-006, the proportion of pseudophakic patients was 41.6% in the ocriplasmin group and 27.1% in the placebo group); in TG-MV-007, the proportion was 33.1% in the ocriplasmin group and 29.6% in the placebo group.

Table 3 Summary of Patient Demographics for the Full Analysis Set (Studies TG-MV-006 and TG-MV-007)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
TG-MV-006	Multi-centre, randomized, placebo-controlled, double-masked	125 µg single intravitreal injection	219 ocriplasmin 107 placebo	71.3 (18-96) years	Male: 119 (36.5%) Female: 207 (63.5%)
TG-MV-007	Same as above	Same as above	245 ocriplasmin 81 placebo	72 (23-97) years	Male: 104 (31.9%) Female: 222 (68.1%)

Study results

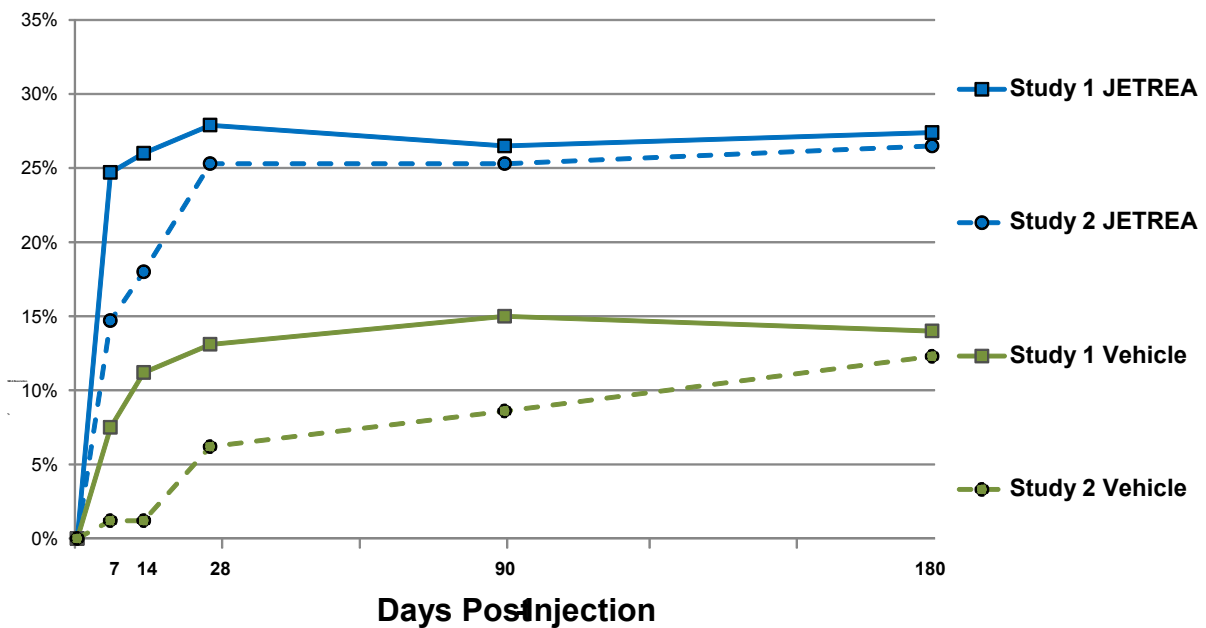
In both of the pivotal studies, the proportion of patients who achieved vitreomacular adhesion (VMA) resolution at Day 28 (i.e. achieved success on the primary endpoint) was significantly higher in the ocriplasmin group compared with the placebo group (Table 4 and Figure 6).

Table 4: Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006 and TG-MV-007: Full Analysis Set)

Treatment Group	TG-MV-006		TG-MV-007	
	Placebo	Ocriplasmin	Placebo	Ocriplasmin
Number of subjects	107	219	81	245
Proportion of subjects with nonsurgical resolution of focal VMA at Day 28	13.1%	27.9%	6.2%	25.3%
Difference (95% CI) p-value	-	14.8 (6.0, 23.5) p= 0.003	-	19.1 (11.6, 26.7) p < 0.001

*Subjects who discontinued the trial prior to visit 'Day 28' or had missing data at visit 'Day 28' were considered based on the last value carried forward method.

Figure 6: Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006 (Study 1) and TG-MV-007 (Study 2))



*Study 1: TG-MV-006; Study 2: TG-MV-007

Total posterior vitreous detachment (PVD) induction in symptomatic vitreomacular adhesion patients was evaluated by B-scan ultrasound. A statistically significantly higher percentage of JETREA treated patients achieved total PVD at Day 28 compared to vehicle treated patients in TG-MV-006 (16% vs. 6%) and in TG-MV-007 (11% vs. 0%).

JETREA treated patients were less likely to require vitrectomy, at the discretion of treating physician, by the end of the study (Month 6) compared with placebo treated patients (TG-MV-006: 20.5% vs 29.0%, respectively; TG-MV-007: 23.5% vs. 15.1%, respectively).

The number of patients with ≥ 2 lines and ≥ 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to vehicle in both trials, however, the number of patients with ≥ 2 lines and ≥ 3 lines decrease in visual acuity was also higher in the ocriplasmin group in one of the studies (Table 5).

Table 5: The Proportion of Subjects with Categorical Change from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (TG-MV-006 and TG-MV-007)

	TG-MV-006		TG-MV-007	
	JETREA N=219	Placebo N=107	JETREA N=245	Placebo N=81
≥ 2 lines Improvement	66 (30.1%)	18 (16.8%)	64 (26.1%)	14 (17.5%)
≥ 3 lines Improvement	28 (12.8%)	9 (8.4%)	29 (11.8%)	3 (3.8%)
≥ 2 lines Worsening	22 (10.0%)	5 (4.7%)	14 (5.7%)	6 (7.5%)
≥ 3 lines Worsening	16 (7.3%)	2 (1.9%)	10 (4.1%)	4 (5.0%)

DETAILED PHARMACOLOGY

Pharmacodynamics

(see ACTION AND CLINICAL PHARMACOLOGY)

Pharmacokinetics

(see ACTION AND CLINICAL PHARMACOLOGY)

TOXICOLOGY

No carcinogenicity, mutagenicity or reproductive and developmental toxicity data are available.

The intravitreal toxicity of ocriplasmin has been evaluated in rabbits, monkeys and minipigs. Ocriplasmin induced an inflammatory response and transient ERG changes in rabbits and monkeys, while no inflammation or ERG changes were observed in minipigs. In rabbits and monkeys, the incidence of vitreous cell infiltrates tended to resolve over time. In monkeys, after administration of 125 $\mu\text{g}/\text{eye}$ (68 $\mu\text{g}/\text{mL}$ vitreous) the ERG was fully recovered by Day 55.

Lens subluxation was observed in the 3 animal species (monkey, rabbit, and minipig) following a single intravitreal injection at high ocriplasmin concentrations at or above 41 $\mu\text{g}/\text{mL}$ vitreous, a concentration above the intended clinical concentration of 29 $\mu\text{g}/\text{mL}$. This effect appeared to be related to the relative size of the species' eye, being more prevalent in smaller eyes, but was observed in all animals that received more than one administration of intravitreal ocriplasmin. Administration of a second intravitreal dose in monkeys, 28 days apart, produced lens

subluxation in 100% of the treated eyes.

Pathological changes related to intraocular hemorrhage were observed in rabbits and monkeys. It remains unclear if this hemorrhage is related to the injection procedure itself or administration of ocriplasmin.

No systemic toxicity was observed after intravitreal administration of ocriplasmin.

The systemic toxicity of ocriplasmin has been evaluated in both rat and dog. Intravenous administration of 10 mg/kg was generally well tolerated in both rat and dog whether administered as a single dose or as repeated doses.

REFERENCES

1. Gandorfer A, Rohleder M, Sethi C, Eckle D, Welge-Lussen U, Kampik A, Luthert P and Charteris D. Posterior Vitreous Detachment Induced by Microplasmin. *Invest Ophthalmol Vis Sci*. 2004;45(2):641-47.
2. Stalmans P, Benz MS, Gandorfer A, et al. Enzymatic Vitreolysis with Ocriplasmin for Vitreomacular Traction and Macular Holes. *N Engl J Med*. 2012;367:606-615.

PART III: CONSUMER INFORMATION

Pr **JETREA**[®]
ocriplasmin solution for intravitreal injection

This leaflet is part III of a three-part "Product Monograph" published when JETREA[®] (je-TRAY-ah) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JETREA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATIONWhat the medication is used for:

JETREA is a concentrate for solution for injection. After dilution, it is injected into the eye.

JETREA is used to treat adults with an eye condition called symptomatic vitreomacular adhesion (VMA).

VMA is caused by persistent vitreous (jelly like material in the back of the eye) attachment to the macula (centre of the light sensitive layer in the back of the eye). The macula provides central vision that is needed for everyday tasks such as driving, reading and recognising faces. VMA can cause symptoms such as distorted or decreased vision. When the condition progresses the adhesion may cause traction, which may eventually result in the formation of a hole in the macula (called macular hole).

What it does:

JETREA works by separating the vitreous humour from the macula.

When it should not be used:

JETREA should not be used if you are allergic to ocriplasmin or any of the other ingredients of this medicine or if you have or are suspected of having an infection in or around your eye.

What the medicinal ingredient is:

The medicinal ingredient in JETREA is ocriplasmin.

What the important nonmedicinal ingredients are:

The nonmedicinal ingredients are: citric acid, mannitol, sodium hydroxide and water.

What dosage forms it comes in:

JETREA is a solution for intravitreal injection after dilution. JETREA is supplied in a glass vial with a latex-free rubber stopper. Each vial contains 0.5 mg of ocriplasmin in 0.2 mL of solution. After dilution with 0.2 mL of 0.9% w/v sodium chloride, 0.1 mL of the diluted solution contains 0.125 mg of ocriplasmin.

WARNINGS AND PRECAUTIONS

BEFORE you use JETREA talk to your doctor or pharmacist if:

- you have or have had any eye conditions or eye treatments.
- you have any allergies to this drug or its ingredients or components of the container.

JETREA is administered as an injection into the eye. Your doctor/ophthalmologist will monitor you in case you develop an infection or any complications after the injection. You should contact your doctor/ophthalmologist immediately if you develop any of the eye symptoms described in section 4 'Possible side effects', after an injection of JETREA.

Driving and using machines

JETREA can cause side effects that may impair your vision. Do not drive or use machines until your vision is clear.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor/ophthalmologist if you are taking, have recently taken or might take any other medicines. Inform your doctor/ophthalmologist if you have had an injection of a medicine into the eye recently. This information will be taken into account to evaluate if and when JETREA can be injected into the same eye.

PROPER USE OF THIS MEDICATIONUsual dose:

You will not be administered JETREA into both eyes at the same time.

You will not be administered JETREA more than once into the same eye.

Overdose:

If an overdose occurs, your doctor/ophthalmologist will monitor you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor/ophthalmologist immediately if you develop any of the following symptoms after an injection with JETREA. Your doctor/ophthalmologist will monitor you and take corrective measures if needed.

- A severe decrease in vision
 - This has been reported in up to 1 in 10 patients within one week after JETREA treatment. This is generally reversible and will usually disappear without treatment.

- Symptoms such as eye pain, worsening eye redness, severely blurred or decreased vision, increased sensitivity to light or increased number of dark floating spots in the field of vision (floaters), increase tear production are also seen in up to 1 in 10 patients.
 - These may be the signs of an infection, bleeding, separation or tear of the retina or an increase in the pressure inside the treated eye.
- Symptoms such as fluctuation of vision, double vision, night blindness, headache, halos around light, nausea and vomiting have been reported in up to 1 in 100 patients and may be the signs of a displacement or wobbling of the lens in the eye from its normal position.

Some tests and imaging of the back of the eye (retina) have been found to be abnormal after Jetrea administration. Your doctor will be aware of this and will take it into account when monitoring your eye.

This is not a complete list of side effects. For any unexpected effects while taking JETREA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in a freezer at $-20^{\circ}\text{C}\pm 5^{\circ}\text{C}$. If the product is exposed to higher temperatures during storage, the vial should be discarded.

The solution should be used immediately after dilution. The vial and any unused portion of the diluted solution should be discarded after single use.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.jetrea.ca/monograph> or by contacting the sponsor, ThromboGenics N.V. at: 1-800-318-0387.

This leaflet was prepared by ThromboGenics N.V.

Last revised: [month day, year]