

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

JETREA 0.5 mg/0.2 ml concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.5 mg of ocriplasmin* in 0.2 ml solution.
After dilution with 0.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, 0.1 ml of the diluted solution contains 0.125 mg ocriplasmin.

*Ocriplasmin is a truncated form of human plasmin produced by recombinant DNA technology in a *Pichia pastoris* expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection (sterile concentrate).
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns (see section 5.1).

4.2. Posology and method of administration

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

Posology

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. Each vial should only be used once and for the treatment of a single eye. Treatment with JETREA in the other eye is not recommended concurrently or 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 in the same eye is not recommended (see section 4.4).

See section 4.4 for instructions on post-injection monitoring.

Special populations

Renal impairment

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 (see section 5.2).

Hepatic impairment

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 (see section 5.2).

Elderly

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

Paediatric population

The safety and efficacy of JETREA in the paediatric population in vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns have not been established. No data are available.

Ethnicity

Experience is limited in groups other than Caucasians.

Method of administration

Single use vial for intravitreal use only.

Preoperative antibiotic drops may be administered at the discretion of the treating ophthalmologist.

Precautions to be taken before handling or administering the medicinal product

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad spectrum topical microbiocide should be administered prior to the injection according to standard medical practice.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active or suspected ocular or periocular infections.

4.4. Special warnings and precautions for use

Post-injection monitoring

JETREA is administered by intravitreal injection only. Intravitreal injections have been associated with intraocular inflammation/infection, intraocular haemorrhage and increased intraocular pressure (IOP). Proper aseptic injection techniques must always be used. Following the intravitreal injection, patients should be monitored for any side effects such as (but not limited to) intraocular inflammation/infection and elevation in IOP. Transient increases in IOP including transient blindness and non-perfusion of the optic nerve have been seen within 60 minutes of injection of JETREA. Monitoring for increases in IOP may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Intraocular inflammation/infection may be assessed using biomicroscopy between 2 and 7 days following the injection. Patients should be instructed to report symptoms suggestive of intraocular inflammation/infection or any other visual or ocular symptoms without delay. If any of the above events occur the patient should be treated according to standard medical practice.

Other warnings and precautions

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

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

There are no clinical data on concomitant use of ocriplasmin with VEGF-inhibitors.

JETREA has not been studied in patients with large diameter macular holes (> 400 microns), high myopia (> 8 dioptre spherical correction or axial length > 28 mm), aphakia, history of rhegmatogenous 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 haemorrhage. Treatment is not recommended in such patients.

The potential for lens subluxation or phacodonesis cannot be ruled out (see section 4.8 and 5.3).

There is limited experience in patients with non-proliferative diabetic retinopathy or history of uveitis (including active severe inflammation) or significant eye trauma. Caution should be exercised when treating such patients.

The effect of ocriplasmin (particularly in inducing resolution of vitreomacular adhesion or causing total posterior vitreous detachment [PVD]) is reduced in subjects with an epiretinal membrane (ERM) or a diameter of VMA > 1500 microns (see section 5.1).

Due to a potential increase in tractional forces, there is a risk of occurrence of new or enlarged macular holes (see section 4.8).

There is a risk for a significant, but transient loss of visual acuity during the first week after the injection. Patients should be monitored appropriately (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Ocriplasmin is a proteolytic enzyme with serine protease activity which could be present in the eye for several days after intravitreal injection (see section 5.2). 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.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of JETREA in pregnant women. No reproductive toxicology studies have been performed. The systemic exposure of JETREA is expected to be very low after intravitreal injection. JETREA should be used during pregnancy only if the clinical benefit outweighs the potential risks.

Breast-feeding

It is unknown whether JETREA is excreted in human milk. JETREA should be used during breast-feeding only if the clinical benefit outweighs the potential risks.

Fertility

There are no data on the effect of JETREA on fertility.

4.7. Effects on ability to drive and use machines

The intravitreal injection of JETREA may be followed by temporary visual disturbances (see section 4.8). In these cases, patients should not drive or use machines until the visual disturbances have resolved.

4.8. Undesirable effects

Summary of the safety profile

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

All adverse reactions were ocular. The most commonly reported were vitreous floaters, eye pain and photopsia, as well as conjunctival haemorrhage resulting from the injection procedure. Most of the adverse reactions occurred within the first week after the injection. The majority of these reactions were non-serious, mild in intensity and resolved within 2 to 3 weeks.

The incidence of serious adverse reactions that occurred in all clinical studies was 2.2% in JETREA treated patients and 2.4% in control patients.

Tabulated list of adverse reactions

The following table summarises the adverse reactions that occurred in clinical studies with a reasonable possibility of causality to the injection procedure or JETREA.

The adverse reactions are listed by MedDRA system organ class and frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing clinical importance.

Eye disorders	Very common Vitreous floaters, eye pain, conjunctival haemorrhage
	Common Visual acuity reduced*, visual impairment, vision blurred, retinal haemorrhage, vitreous haemorrhage, retinal tear*, retinal detachment*, intraocular pressure increased, macular hole*, macular degeneration, retinal degeneration, macular oedema, retinal oedema, retinal pigment epitheliopathy, metamorphopsia, vitreous adhesions*, conjunctival oedema, eyelid oedema, vitritis, anterior chamber cell, anterior chamber flare, iritis, photopsia, conjunctival hyperaemia, ocular hyperaemia, vitreous detachment, retinogram abnormal*, eye irritation, dry eye, foreign body sensation in eyes, eye pruritus, ocular discomfort, photophobia, chromatopsia*
	Uncommon Transient blindness, lens subluxation*, scotoma, visual field defect, diplopia, hyphaema, miosis, pupils unequal, corneal abrasion, anterior chamber inflammation, eye inflammation, conjunctival irritation

* see section 'Description of selected adverse reactions'

Description of selected adverse reactions

Visual acuity reduced

In the placebo-controlled pivotal phase III studies, 7.7% of JETREA patients and 1.6% of placebo patients had acute transient ≥ 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. Visual acuity

decreases were generally reversible within 2 weeks without intervention. See section 4.4 for monitoring recommendations.

Chromatopsia

Dyschromatopsia (generally described as yellowish vision) has been reported as a common adverse reaction in patients injected with JETREA. The majority of events were non-serious, mild and generally resolved spontaneously. The median time to resolution was 3 months.

Retinogram abnormal

Electroretinographic (ERG) changes (a- and b-wave amplitude decrease) have been reported as a common adverse reaction in patients injected with JETREA; in the majority of cases dyschromatopsia was also reported. In approximately half of the 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.

Retinal breaks (tears and detachment)

In the placebo-controlled pivotal phase III studies, 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 detachment that occurred pre-vitrectomy was 0.4% in the JETREA group and none in the placebo group, while the incidence of retinal tears (without detachment) that occurred pre-vitrectomy was 0.2% in the JETREA group and 0.5% in the placebo group.

Macular hole

In the placebo-controlled pivotal phase III studies, cases of new onset or worsening of macular hole were reported for 6.7% of all patients injected with JETREA vs. 9.6% injected with placebo. Although in placebo-controlled pivotal phase III studies, JETREA has shown benefit in inducing closure of macular holes associated with vitreomacular traction, in some instances increased traction with subsequent progression or development of new macular hole has been observed. Development of these events is part of natural disease progression; however, a contribution of ocriplasmin in some cases appears plausible based upon its mechanism of action.

Vitreous adhesions

In the placebo-controlled pivotal phase III studies, cases of worsening of vitreomacular adhesion/vitreomacular traction were reported for 1.5% of all patients injected with JETREA vs. 1.1% injected with placebo. Development of these events is part of natural disease progression; however, a contribution of ocriplasmin in some cases appears plausible based upon its mechanism of action.

Lens subluxation/phacodonesis

One case of lens subluxation/phacodonesis was reported in clinical studies in adults and appears to have been possibly related to treatment with JETREA. In a paediatric study evaluating JETREA as an adjunct to vitrectomy, one case of subluxation was reported in a premature infant who received a single intravitreal injection of JETREA 0.175 mg. Lens subluxation was observed in 3 animal species at ocriplasmin concentrations above the intended clinical concentration (see section 5.3).

Based on the proteolytic activity of ocriplasmin, preclinical and clinical findings, the potential for lens subluxation or phacodonesis cannot be ruled out. If this event occurs, it should be treated according to standard medical practice.

See section 4.4 for monitoring recommendations. Routine observation is recommended in all above situations.

4.9. Overdose

The clinical data on the effects of JETREA overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) has been reported. The patient had a decrease in BCVA of 21 ETDRS letters from baseline that returned to within 9 letters of baseline at the end of the

study. The patient also developed mild conjunctival hyperaemia, eye inflammation and miosis which resolved with corticosteroid eye drops.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: **not yet assigned**, ATC code: **not yet assigned**.

Mechanism of action

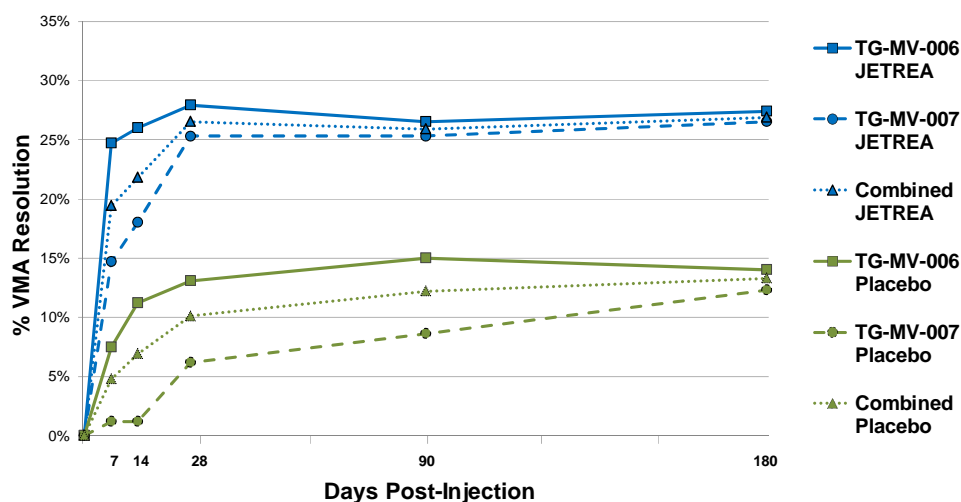
Ocriplasmin has a proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) (e.g. laminin, fibronectin and collagen) and aims to dissolve the protein matrix responsible for the abnormal vitreomacular adhesion (VMA). The tight binding of the protein components within the macular area of the VRI contribute to vitreomacular traction (VMT), leading to visual impairment and/or macular holes.

Clinical efficacy and safety

The efficacy of JETREA was demonstrated in 2 multicentre, randomised, double-masked, placebo-controlled, 6-month studies in patients with VMT. A total of 652 patients (JETREA 464, placebo 188) were randomised in these 2 studies (TG-MV-006 and TG-MV-007).

In both pivotal studies, the proportion of patients who achieved VMA resolution at Day 28 (primary endpoint) was significantly ($p \leq 0.003$) higher in the JETREA group compared with the placebo group. The difference continued to be statistically significant through Month 6 in each study ($p \leq 0.024$). In the integrated data, 26.5% in the JETREA group compared with 10.1% in the placebo group achieved VMA resolution at Day 28 ($p < 0.001$). The difference was maintained from Day 7 through Month 6 (Figure 1).

Figure 1: Proportion of patients with VMA resolution up to Day 180 (Month 6) (TG-MV-006, TG-MV-007 and integrated data)



At all post-injection days, $p \leq 0.024$ in TG-MV-006, $p \leq 0.009$ in TG-MV-007, $p < 0.001$ in integrated data

Patients with no ERM at baseline were more likely to achieve VMA resolution at Day 28 compared with those who had ERM at baseline. In the integrated data, the VMA resolution rate at Day 28 was higher in patients treated with JETREA compared to placebo in both the subgroup without ERM (37.4% vs. 14.3%, $p < 0.001$) and with ERM (8.7% vs. 1.5%, $p = 0.046$).

Patients with a smaller VMA diameter at baseline (≤ 1500 microns) were more likely to achieve VMA resolution at Day 28 compared with those who had a diameter > 1500 microns. In the integrated data, the VMA resolution rate at Day 28 was higher in patients treated with JETREA compared to placebo in both the subgroup with VMA ≤ 1500 microns at baseline (34.7% vs. 14.6%, $p < 0.001$) and with VMA > 1500 microns at baseline (5.9% vs. 0%, $p = 0.113$).

In the integrated data, 106 (22.8%) and 47 (25%) in the JETREA and placebo groups respectively had full thickness macular hole (FTMH) at baseline. Of these, the proportion of patients who achieved FTMH closure without vitrectomy at Day 28 was higher in the JETREA group than the placebo group (40.6% vs. 10.6%, respectively; $p < 0.001$). A difference was maintained through the end of the studies (Month 6).

A significantly higher percentage of JETREA treated patients experienced total PVD at Day 28 compared to placebo treated patients (integrated data: 13.4% vs. 3.7%, respectively; $p < 0.001$).

During the studies, vitrectomy could be performed at the discretion of the Investigator. JETREA treated patients were less likely to have had a vitrectomy by the end of the study (Month 6) compared with placebo treated patients (integrated data: 17.7% vs. 26.6%, respectively; $p = 0.016$).

A higher proportion of JETREA treated patients gained ≥ 2 or ≥ 3 lines in BCVA (irrespective of vitrectomy) at Month 6 (28.0% and 12.3%, respectively) compared with patients treated with placebo (17.1% and 6.4%) ($p = 0.003$ and $p = 0.024$, respectively). Also the proportion of patients gaining ≥ 2 or ≥ 3 lines in BCVA without vitrectomy favoured JETREA at Month 6 (23.7% vs. 11.2%, $p < 0.001$ for a gain ≥ 2 lines and 9.7% vs. 3.7%, $p = 0.008$ for a gain ≥ 3 lines).

In the integrated analysis of the National Eye Institute Visual Function Questionnaire-25 (VFQ-25), a numerical favour of JETREA over placebo was shown in each sub-scale score, as well as the composite score. The difference for improvement in the general vision sub-scale score was statistically significant (6.1 JETREA vs. 2.1 placebo, $p = 0.024$).

The European Medicines Agency has waived the obligation to submit the results of studies with JETREA in all subsets of the paediatric population in the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties

Ocriplasmin levels in the vitreous decrease rapidly after intravitreal administration. In a clinical study in patients scheduled for vitrectomy receiving 0.125 mg JETREA (corresponding to a theoretical start concentration of 29 $\mu\text{g/ml}$ vitreous), mean ocriplasmin activity was 9% of theoretical start concentration 2-4 hours after injection and below the lower level of quantification at 7 days.

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

When administered intravenously, ocriplasmin enters the endogenous protein catabolism pathway through which it is rapidly inactivated via its interactions with protease inhibitor α_2 -antiplasmin or α_2 -macroglobulin. The inactive ocriplasmin/ α_2 -antiplasmin complex is cleared from the circulation with a half-life ($t_{1/2}$) of several hours.

Renal impairment

No studies have been conducted to examine the pharmacokinetics of ocriplasmin in patients with renal impairment since the systemic exposure is expected to be very low after intravitreal administration.

Hepatic impairment

No studies have been conducted to examine the pharmacokinetics of ocriplasmin in patients with hepatic impairment since the systemic exposure is expected to be very low after intravitreal administration.

5.3. Preclinical safety data

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 µg/eye (68 µg/ml vitreous) the ERG was fully recovered by Day 55. Lens subluxation was observed in the 3 species at ocriplasmin concentrations at or above 41 µg/ml vitreous, a concentration above the intended clinical concentration of 29 µg/ml. This effect appeared to be dose-related and was observed in all animals administered intravitreal ocriplasmin more than once. Pathological changes related to intraocular haemorrhage were observed in rabbits and monkeys. It remains unclear if this haemorrhage 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 single dose or as repeated dose.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol
Citric acid
Sodium hydroxide (pH adjustment)
Water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, other than sterile, preservative-free, non-buffered diluent sodium chloride 9 mg/ml (0.9%) solution for injection.

6.3. Shelf life

18 months

After dilution:

From a microbiological point of view, the product should be used immediately.
The vial and any unused portion of the diluted solution should be discarded after single use.

6.4. Special precautions for storage

Store in a freezer (-20°C ±5°C). If the product is exposed to higher temperatures during storage, the vial should be discarded.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

0.2 ml solution in a vial (type I glass) closed with a latex-free chlorobutyl rubber stopper. Pack containing 1 vial.

6.6. Special precautions for disposal and other handling

Vials are for single use only.

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

1. Remove the vial from the freezer and allow to thaw at room temperature (takes about 2 minutes).
2. Once completely thawed, remove the protective polypropylene flip-off cap from the vial.
3. Disinfect the top of the vial 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 and gently swirl the vial until the solutions are mixed. 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. The diluted solution should be used immediately as it contains no preservatives.
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 incline the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.
7. Replace the needle with an appropriate sterile needle, carefully expel the air from the syringe and adjust the dose to the 0.1 ml mark on the syringe (corresponding to 0.125 mg ocriplasmin).
8. Inject 0.1 ml of the diluted solution immediately into the mid-vitreous as it contains no preservatives.
9. Discard the vial and any unused portion of the diluted solution after single use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ThromboGenics NV
Gaston Geenslaan 1
B-3001 Leuven
Belgium

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED
Belasis Avenue
Billingham, Cleveland
TS23 1LH
United Kingdom

Name and address of the manufacturer(s) responsible for batch release

ThromboGenics NV
Gaston Geenslaan 1
B-3001 Leuven
BELGIUM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where JETREA will be marketed, at launch and after launch, all healthcare professionals who are expected to use JETREA are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Information packs for the patients

The patient information pack should be provided in printed and in audio format, and contain the following key elements:

- Patient information leaflet
- How to prepare for Jetrea treatment
- How is Jetrea treatment administered
- What are the steps following treatment with Jetrea
- Key signs and symptoms of serious adverse events
- When to seek urgent attention from the health care provider

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

JETREA 0.5 mg/0.2 ml concentrate for solution for injection
Ocriplasmin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 mg ocriplasmin. After dilution, 0.1 ml contains 0.125 mg ocriplasmin.

3. LIST OF EXCIPIENTS

Mannitol, citric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Intravitreal use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a freezer.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ThromboGenics NV
Gaston Geenslaan 1
B-3001 Leuven
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

JETREA 0.5 mg/0.2 ml sterile concentrate
Ocriplasmin
Intravitreal use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the patient

JETREA 0.5 mg/0.2 ml concentrate for solution for injection Ocriplasmin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Jetrea is and what it is used for
2. What you need to know before you are given Jetrea
3. How Jetrea is given
4. Possible side effects
5. How Jetrea is stored
6. Contents of the pack and other information

1 What Jetrea is and what it is used for

Jetrea contains the active substance ocriplasmin.

Jetrea is used to treat adults with an eye disease called vitreomacular traction (VMT), including when it is associated with a small hole in the macula (central part of the light-sensitive layer at the back of the eye).

VMT is caused by traction resulting from a persistent attachment of the vitreous humour (jelly-like material in the back of the eye) to the macula. The macula provides central vision that is needed for everyday tasks such as driving, reading and recognising faces. VMT can cause symptoms such as distorted or decreased vision. When the disease progresses the traction may eventually result in the formation of a hole in the macula (called a macular hole).

Jetrea works by separating the vitreous humour from the macula, and helping to close the macular hole if one is present, which may decrease the symptoms caused by VMT.

2 What you need to know before you are given Jetrea

You must not be given Jetrea

- if you are allergic to ocriplasmin or any of the other ingredients of this medicine (listed in section 6);
- if you have (or suspect you may have) an infection in or around your eye.

Warnings and precautions

Talk to your doctor/ophthalmologist before you are given Jetrea.

Jetrea is given 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.

You will not be given Jetrea into both eyes at the same time.

You will not be given Jetrea more than once into the same eye.

Tell your doctor/ophthalmologist if you have or have had any eye conditions or eye treatments. Your doctor/ophthalmologist will decide if treatment with Jetrea is right for you.

Children and adolescents

Jetrea should not be used in children and adolescents below 18 years old due to the lack of data in this patient group.

Other medicines and Jetrea

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.

Pregnancy and breast-feeding

There is no experience of using Jetrea in pregnant women or during breast-feeding. Jetrea should not be used during pregnancy or breast-feeding unless your doctor/ophthalmologist thinks it is clearly necessary. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor/ophthalmologist for advice before being given this medicine.

Driving and using machines

After Jetrea treatment you may experience some decrease in vision for a limited amount of time. If this happens, do not drive or use any tools or machines until your vision improves.

3 How Jetrea is given

Jetrea must be given by a qualified ophthalmologist (eye specialist) who has experience in giving injections into the eye.

Jetrea is given as a single injection into the affected eye. The recommended dose is 0.125 mg.

Your doctor/ophthalmologist may ask you to use antibiotic eye drops before and after the injection in order to prevent any possible eye infection.

On the day of the injection, your doctor/ophthalmologist will use antimicrobial eye drops and clean your eye and eyelid carefully to prevent infection. Your doctor/ophthalmologist will also give you a local anaesthetic to prevent any pain from the injection.

After the injection, your doctor/ophthalmologist will monitor your vision.

If you have any further questions on the use of this medicine, ask your doctor/ophthalmologist.

4 Possible side effects

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 injection of Jetrea. Your doctor/ophthalmologist will monitor you and take corrective measures if needed.

- A **severe** decrease in vision has been reported in up to 1 in 10 patients within one week after Jetrea treatment. This is generally reversible and will usually disappear within two weeks.
- 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) are also seen in up to 1 in 10 patients and 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, 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.

Talk to your doctor/ophthalmologist if you develop any of the additional side effects listed below:

Very common side effects (may affect more than 1 in 10 patients):

- bleeding on the surface of the eye

Common side effects (may affect up to 1 in 10 patients):

- visual disturbances
- bleeding inside the eye
- blind spot or blind area in the field of vision
- distorted vision
- swelling of the surface of the eye
- swelling of the eyelid
- inflammation of the eye
- flashes of light in the eye
- irritation on the surface of the eye
- dry eye
- a feeling of having something in the eye
- itching of the eye
- eye discomfort
- colour vision changes

Uncommon side effects (may affect up to 1 in 100 patients):

- decreased vision in parts of the field of view
- accumulation of blood in the front part of the eye
- abnormal constriction of the pupil (black part in the centre of the eye)
- different sized pupils
- a scratch or scrape of the cornea (transparent layer that covers the front of the eye)

If you get any side effects, talk to your doctor/ophthalmologist. This includes any possible side effects not listed in this leaflet.

5 How Jetrea is stored

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 (-20°C ±5°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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 Contents of the pack and other information

What Jetrea contains

- The active substance is ocriplasmin. One vial of Jetrea contains 0.5 mg of ocriplasmin in 0.2 ml solution. After dilution with 0.2 ml of sodium chloride solution, 0.1 ml of the diluted solution contains 0.125 mg of ocriplasmin.
- The other ingredients are mannitol, citric acid, sodium hydroxide and water for injections.

What Jetrea looks like and contents of the pack

Jetrea is a concentrate for solution for injection in a vial. The concentrate is clear and colourless. Each pack contains one vial.

Marketing Authorisation Holder and Manufacturer

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For any information about this medicine, please contact the local representative of the marketing Authorisation Holder:

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This leaflet was last revised in**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

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

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. Each vial should only be used once and for the treatment of a single eye. Treatment with Jetrea in the other eye is not recommended concurrently or 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 in the same eye is not recommended.

See section 4.4 of the Summary of Product Characteristics for instructions on post-injection monitoring.

Single use vial for intravitreal use only.

Preoperative antibiotic drops may be administered at the discretion of the treating ophthalmologist.

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad spectrum topical microbiocide should be administered prior to the injection according to standard medical practice.

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

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

1. Remove the vial from the freezer and allow to thaw at room temperature (takes about 2 minutes).
2. Once completely thawed, remove the protective polypropylene flip-off cap from the vial (**Figure 1**).
3. Disinfect the top of the vial with an alcohol wipe (**Figure 2**).
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 (**Figure 3**) and gently swirl the vial until the solutions are mixed (**Figure 4**). 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. The diluted solution should be used immediately as it contains no preservatives.
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 incline the vial to ease withdrawal) (**Figure 5**) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.
7. Replace the needle with an appropriate sterile needle, carefully expel the air from the syringe and adjust the dose to the 0.1 ml mark on the syringe (corresponding to 0.125 mg ocriplasmin) (**Figure 6**).
8. Inject 0.1 ml of the diluted solution immediately into the mid-vitreous as it contains no preservatives.
9. Discard the vial and any unused portion of the diluted solution after single use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

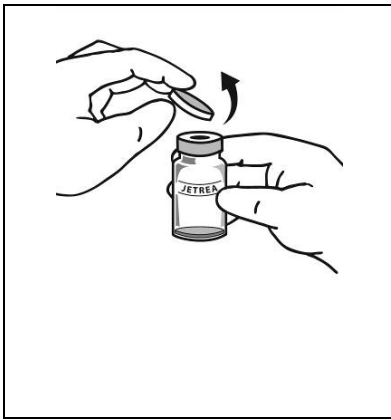


Figure 1

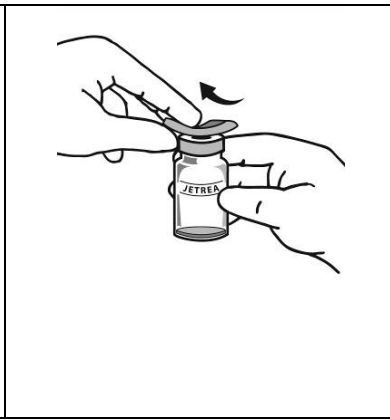


Figure 2

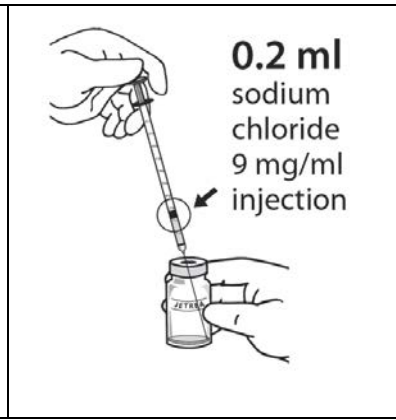


Figure 3

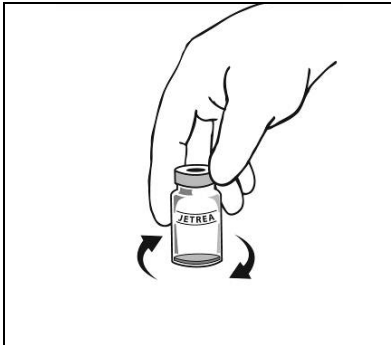


Figure 4

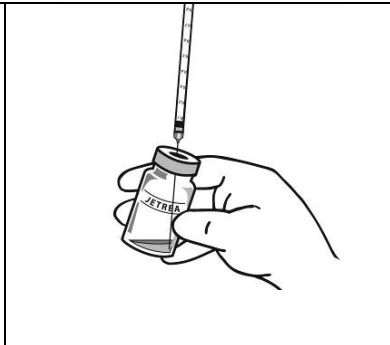


Figure 5

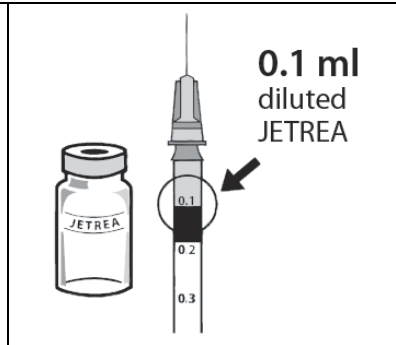


Figure 6