

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Management Review

Date: October 4, 2012

Reviewer: Mary Dempsey, B.S., Risk Management Reviewer
Division of Risk Management (DRISK)

Cynthia LaCivita, Pharm. D., Risk Management Analyst
Team Leader, DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): Jetrea (ocriplasmin) Intravitreal Injection

Dosage and Route: 2.5 mg/mL intervitreal injection

Application Type/Number: BLA 125422

Applicant/sponsor: ThromboGenics, Inc.

OSE RCM #: 2012-2296

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the Biologic License Application (BLA) 125422 for Jetrea (ocriplasmin). On April 17, 2012, the Division of Transplant and Ophthalmology Products (DTOP) received this BLA submission with a proposed indication for the treatment of symptomatic vitreomacular adhesion (VMA) including macular hole.

This compound is being developed by ThromboGenics, Inc.

The applicant is seeking approval based on two phase 3 trials (TG-MV-006 and TG-MV-007). Both trials were multicenter, randomized, placebo controlled, double-masked, 6 month studies conducted in the U.S. and Europe.

The applicant did not submit a proposed REMS or risk management plan.

2. BACKGROUND

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 kDa.

The drug product is a sterile, clear and colorless solution with no preservatives in a single use glass vial containing 0.5 mg of ocriplasmin in 2.5 mg/mL solution for intravitreal injection after dilution.

For intravitreal administration, dilution with 0.2 mL sodium chloride (0.9% w/v) solution for injection is required. The recommended dose is a single intravitreal injection of 0.125 mg (125 µg) corresponding to 0.1 mL of the diluted solution. The proposed indication is for the treatment of symptomatic VMA including macular hole.

Currently, there are no pharmacological treatment options for patients with symptomatic VMA including macular hole, and the only available treatment option is vitrectomy, a surgical procedure. The current standard of care for patients with symptomatic VMA is either “watchful waiting” or vitrectomy. Ocriplasmin was developed as an alternative for an invasive procedure which carries risks such as retinal tears/detachments, endophthalmitis, etc. Ocriplasmin is not marketed in any country.

Ocriplasmin is a serine protease shown to cleave both physiological substrates (such as fibronectin, fibrinogen, collagen, laminin, gelatin, ocriplasmin etc) as well as synthetic peptide substrates (such as S-2403 and S-2444). Following intravitreal administration, the

proteolytic activity of ocriplasmin is purported to help in dissolution of the vitreal matrix proteins at the abnormal vitreoretinal interface focal points thereby resolving or reducing the complications associated with VMA.

3. REGULATORY HISTORY

(b) (4)

- April 17, 2012 ThromboGenics submitted BLA 125422 and requested Priority Review

4. MATERIAL REVIEWED

- April 17, 2012 original BLA 125422
- July 26, 2012 Dermatologic and Ophthalmic Drugs Advisory Committee minutes
- September 26, 2012 Clinical Review by Jennifer D. Harris, M.D.

5. REVIEW OF RISK MANAGEMENT OPTIONS

The applicant did not submit a proposed REMS or a risk management plan for this product.

5.1. OVERVIEW OF CLINICAL PROGRAM

The safety and efficacy of ocriplasmin for the treatment of VMA was evaluated in two phase 3 trials (TG-MV-006 and TG-MV-007). Both trials were multicenter, randomized, placebo controlled, double-masked, 6 month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA.

A total of 652 patients (ocriplasmin 464, placebo 188) were randomized in these two studies. The 125µg dose was associated with the most efficacy in both studies with no additional benefit observed with the 175µg dose or repeat injections of 125µg. The efficacy of this product was based on an anatomical endpoint of complete VMA resolution as documented by optical coherence topography (OCT). The clinical benefit of this anatomical finding has been documented in the literature. Ocriplasmin is not recommended for the treatment of full thickness macular holes (FTMH) associated with VMA.

Jennifer D. Harris, M.D., the clinical reviewer, concluded the following:

- 1) ocriplasmin is statistically superior to placebo in both of the phase 3 trials for all of the analysis sets
- 2) the percentage of macular hole closure in both of the phase 3 trials is numerically greater in the ocriplasmin treated patients compared to placebo. This difference was **not** statistically significant
- 3) based on the phase 3 trials, approximately 20% of patients successfully treated with ocriplasmin may require vitrectomy surgery.

5.2 SAFETY

A total of 10 sponsor studies and 2 investigator-initiated studies have been conducted for administered ocriplasmin. Seven (7) of those studies were completed at the time of the data cut off date. The safety results from the seven completed clinical trials evaluating intravitreal injection of ocriplasmin were pooled for analyses of AEs and other safety assessments performed during the studies.

The most common adverse reactions (incidence $\geq 5\%$ listed in descending order of frequency) in the pivotal placebo-controlled clinical studies were: vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, retinal edema and macular edema.

The adverse events seen are consistent with the known adverse events associated with intraocular injections, many occur at a much higher rate in the ocriplasmin group which may suggest a drug related effect in addition to the background rate. These events include eye pain, ocular discomfort, and iritis.

The majority of adverse events occurred during the first 7 days after ocular injection. Many of the adverse events occurring at a higher rate during the first 7 days are those commonly associated with intraocular injections such as floaters, eye pain, blurred vision, iritis photophobia and ocular discomfort. Macular edema appears to be a later complication associated with injection of ocriplasmin.

Overall, there was no statistically significant difference in the rate of common adverse events or serious adverse events in the study eye between the ocriplasmin treated patients and placebo.

5.3 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

Studies in pediatric patients are currently ongoing. Completion of the studies will be requested in a post marketing requirement (PMR).

The sponsor currently is conducting an efficacy trial in patients ≤ 16 as an adjunct to conventional vitrectomy. The results of this study should be submitted to this application as a PMR.

5.4 AC STATUS

Ocriplasmin was presented at the July 26, 2012 Dermatologic and Ophthalmic Drugs Advisory Committee. The Advisory Committee was asked six questions regarding the efficacy, need for additional studies, benefit of treatment outweighing potential risks, and product labeling.

The committee unanimously agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of vitreomacular adhesions and unanimously agreed that the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks.

The majority of the committee agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of macular holes associated with vitreomacular adhesions. Additionally, the majority of the committee agreed that substantial evidence has not been provided to demonstrate effective for the treatment of all macular holes regardless of the presence of adhesions.

The majority of the committee agreed that additional studies are not needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina. The Advisory Committee and the clinical reviewer did not recommend risk mitigation measures beyond Professional Labeling (PI) and routine postmarketing pharmacovigilance

6. DISCUSSION

As a result of the AC recommendation and the clinical review, the proposed indication is revised (b) (4) and now reads:

(b) (4)

The current standard of care for patients with symptomatic VMA is either "watchful waiting" or vitrectomy. Ocriplasmin was developed as an alternative for an invasive

procedure. The safety and efficacy of ocriplasmin has been demonstrated and the approval would meet and unmet medical need.

The adverse events observed in clinical testing are consistent with the known adverse events associated with intraocular injections, and such adverse events are routinely managed by ophthalmologists.

The applicant did not submit a REMS or a risk management plan for this product; therefore, the applicant proposes marketing with labeling and routine pharmacovigilance in compliance with reporting requirements for an approved BLA (21 CFR 600.80 and 21.600.81). Dr. Jennifer D. Harris, the FDA clinical reviewer, agreed with the applicant that there are no risks requiring risk mitigation beyond labeling and routine pharmacovigilance.

7. CONCLUSION

At this time, DRISK agrees that labeling and routine pharmacovigilance measures are appropriate for ocriplasmin.

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/s/

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10/04/2012

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10/04/2012
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