

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125422Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Director Decisional Memo

<b>Date</b>	(electronic stamp)
<b>From</b>	Edward Cox, MD MPH
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	BLA # 125422
<b>Supplement #</b>	
<b>Applicant Name</b>	ThromboGenics, Inc.
<b>Date of Submission</b>	April 16, 2012
<b>Date of Receipt</b>	April 17, 2012
<b>PDUFA Goal Date</b>	October 17, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Jetrea Ocriplasmin
<b>Dosage Form</b>	(ophthalmic) intravitreal injection
<b>Dose</b>	0.125 mg (125 µg) in 0.1 mL
<b>How supplied</b>	One single-use 2-mL glass vial containing 0.5 mg ocriplasmin in 0.2 mL solution (2.5 mg/mL) To be diluted with 0.2 mL sodium chloride 0.9% before use (final concentration 0.5 mg/0.4mL, with only 0.1 mL to be dosed)
<b>Proposed Indication(s)</b>	Treatment of symptomatic vitreomacular adhesion
<b>Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Jennifer Harris
Statistical Review	Yunfan Deng, Yan Wang
Pharmacology Toxicology Reviews	Maria Rivera, Amy Ellis, Lori Kotch, Abby Jacobs
Product Quality/OBP Reviews	Jee Chung, Kathy Lee, Ramesh Potla, Nikolay Spiridonov, Richard Ledwidge, Frederick Mills, Maria Gutierrez Lugo, Leslie Rivera Rosado
Product Quality Microbiology	Lakshmi Narasimhan, Patricia Hughes,
OBP Label and Labeling Review	Kimberly Rains, Ramesh Potla
Clinical Pharmacology Review	Yoriko Harigaya, Phil Colangelo
OSI	Kassa Ayalew, Susan Leibenhaut, Susan Thompson
OSE/DMEPA	Jung Lee, Jamie Wilkins Parker, Kellie Taylor, Carol Holquist
CDTL Review	Bill Boyd
Deputy Division Director's Review	Wiley Chambers
Division Director's Review	Renata Albrecht

OND=Office of New Drugs

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

Jetrea (ocriplasmin) is a recombinant, truncated form of human plasmin. In BLA 125422, Jetrea was evaluated for the treatment of symptomatic vitreomacular adhesion (VMA). Symptomatic VMA can develop as the vitreous humor liquefies as part of aging process and can cause traction by the vitreous on the retina. Retinal traction can be associated with visual symptoms in some cases and can also potentially lead to other anatomic sequelae. Ocriplasmin is a proteolytic enzyme that is active against protein components of the vitreoretinal interface, including laminin, fibronectin, and collagen. Through its proteolytic activity, the intended action of ocriplasmin is to dissolve the protein matrix responsible for the VMA.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Jetrea. For a detailed discussion of BLA 125422, the reader is referred to the individual discipline specific reviews. In addition Dr. Boyd's Cross-Discipline Team Leader Review, Dr. Chambers's Deputy Division Director Review, and Dr. Albrecht's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The Product Quality review finds that the manufacturing of Jetrea is well-controlled, and leads to a product that is pure and potent; they recommend approval of Jetrea. There are a number of postmarketing commitments for Jetrea on manufacturing issues including acceptance criteria and product specifications, methods, and other manufacturing issues. As of October 17, 2012, the Compliance assessment is that there are no issues with the manufacturing and testing facilities that preclude approval of this BLA.

The Product Quality microbial control, sterility assurance review recommends approval for Jetrea. The recommendation for approval is accompanied by postmarketing commitments on the (b) (4) and further evaluation of testing methods related to sterility testing.

The recommendation from the pharmacology/toxicology reviewer is for approval. Jetrea is labeled as Pregnancy Category C reflecting that there have not been animal reproductive toxicology studies or studies in pregnant women. The systemic exposure to ocriplasmin is expected to be low after an intravitreal injection. Toxicology studies in three animal species (monkey, rabbit, and minipig) found lens subluxation after a single dose of ocriplasmin at vitreous concentrations 1.4 times higher than human exposures. In a study in monkeys, administration of a second intravitreal dose 28 days after the first dose of ocriplasmin was associated with lens subluxation in 100% of the animals. The Warnings and Precautions section of the product labeling includes a section on the potential for lens subluxation that

includes this information and information from one case in a human that received a single intravitreal injection of 0.175 mg.

The Clinical Pharmacology reviewer finds the data in the application acceptable. The Clinical Pharmacology Reviewer notes that following a single dose of 0.125 mg of ocriplasmin, detectable levels of activity were present in vitreous humor when tested immediately after injection and then decreased with time after injection. The product labeling includes a table of mean ocriplasmin activity levels over time following intravitreal injection. Ocriplasmin is inactivated predominantly by  $\alpha$ 2-antiplasmin. Systemic absorption of ocriplasmin is expected to be minimal.

The applicant submitted results from two, randomized, double-masked, multi-center, vehicle controlled phase 3 trials (studies TG-MV-006 and TG-MV-007) evaluating the safety and efficacy of a single intravitreal dose of Jetrea 0.125 mg of for the treatment of patients with symptomatic vitreomacular adhesion (VMA). The primary efficacy endpoint in these trials was resolution of focal VMA at post-injection Day 28 post-injection. The primary endpoint was determined by optical coherence tomography (OCT) evaluated by a masked central reading center. Review of the literature supports the association of relief of traction with decreased macular edema with subsequent increased visual acuity. (See appendix 9.1 Literature review and reference in the Clinical Review and the appendix in the Summary Review for Regulatory Action.) Study TG-MV-006 enrolled 326 patients [219 randomized to ocriplasmin and 107 randomized to vehicle (2:1 treatment allocation)]. Study TG-MV-007 enrolled 326 patients [245 randomized to ocriplasmin and 81 randomized to vehicle (3:1 treatment allocation)]. In study TG-MV-006 the proportion of ocriplasmin treated patients achieving resolution of VMA was 27.9% vs. 13.1% for vehicle control (treatment difference 14.8%, 95% CI 6.0, 23.5%). In study TG-MV-007 the proportion of ocriplasmin treated patients achieving resolution of VMA was 25.3% vs. 6.2% for vehicle control (treatment difference 19.1%, 95% CI 11.6, 26.7%). The applicant also requested inclusion of the term with macular hole in the indication. As noted in the reviews, the data are not sufficient to support inclusion of macular holes in the indication.

The safety database included 741 patients who received ocriplasmin and 247 control patients. Serious nonfatal adverse reactions of the eye occurred in 37/465 (8%) ocriplasmin and 20/187 (10.7%) placebo patients. Dropouts and discontinuations were seen in 29/465 (6.2%) of ocriplasmin and 16/187 (8.6%) placebo patients. Based on the safety findings from the clinical trials, product labeling includes information in the Warnings and Precautions section on decreased vision, effects of intravitreal injection, potential for subluxation of the lens, retinal breaks, and dyschromatopsia.

The effect on best corrected visual acuity over time by treatment arm was examined in detail. In evaluating changes in best corrected visual acuity there was a trend towards a numerically greater percentage of ocriplasmin treated patients who experience improvements in BCVA at

month 6 (either  $\geq 2$ -line or  $\geq 3$ -line visual acuity). While the numbers are small, there also appears to be a numerically higher percentage of ocriplasmin treated patients in one of the two trials (TG-MV-006) who experience worsening of BCVA (either  $\geq 2$ -line or  $\geq 3$ -line visual acuity) but not in the second trial (TG-MV-007). (See Table 13 in the Summary Review for Regulatory Action and the Figure of Percentage of Patients with Gain (+) or Loss (-) of Visual Acuity). The individual cases of all  $\geq 2$ -line worsening in BCVA were reviewed by the clinical reviewer. The majority of the cases were judged to be related to progression of vitreomacular traction or macular hole. It is important that this information is available to healthcare providers as they consider the risk and benefits of Jetrea and discuss treatment options with their patients. The product labeling for Jetrea includes both a table and a figure that summarize the information on changes in BCVA.

In the vehicle controlled phase 3 trials 76.6% of ocriplasmin-treated patients reported an adverse event compared to 69.0% of vehicle-treated patients. Ocular adverse events were reported by 69.7% of ocriplasmin-treated patients compared to 56.7% of vehicle-treated patients. With regard to ocular adverse events that were numerically higher for ocriplasmin-treated patients were the following: vitreous floaters were reported in 17.6% of ocriplasmin-treated patients reported and 8.6% of vehicle-treated patients; eye pain was reported in 13.3% of ocriplasmin-treated patients reported and 5.9% of vehicle-treated patients; photopsia was reported in 12.0% of ocriplasmin-treated patients reported and 2.7% of vehicle-treated patients; vision blurred was reported in 8.8% of ocriplasmin-treated patients reported and 4.3% of vehicle-treated patients.

The application for Jetrea was presented to the Dermatologic and Ophthalmic Drugs Advisory Committee (AVDAC) on July 26, 2012. On the question of whether substantial evidence of effectiveness had been provided for ocriplasmin 0.125 mg for treatment of vitreomacular adhesions the Committee voted Yes 10; No 0; Abstain 0. On the question of whether substantial evidence of effectiveness had been provided for ocriplasmin 0.125 mg for treatment of macular holes associated with vitreomacular adhesions the Committee voted Yes 7; No 3; Abstain 0. Those voting yes noted that the data was favorable. Those voting No noted that the amount of data was not sufficient. On the question of whether substantial evidence of effectiveness had been provided for ocriplasmin 0.125 mg for treatment of all macular holes regardless of the presence of adhesions the Committee voted Yes 1; No 8; Abstain 1. On the question of whether additional studies are needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina, the Committee voted Yes 3; No 6; Abstain 1. On the question of whether the benefits of administering ocriplasmin for treatment of vitreomacular adhesions outweigh the potential risks, the Committee voted Yes 10; No 0; Abstain 0. The Committee also provided suggestions about information to include in the product labeling.

Inspections of four clinical trial sites (two from each of the phase 3 trials) finds the data from the phase 3 trials appear reliable and can be used in support of the application.

Jetrea was discussed at the Pediatric Review Committee on 10/3/12. Pediatric studies (b) (4)  are deferred because the application is otherwise ready for approval in adults. Thrombogenics currently has an ongoing pediatric study evaluating ocriplasmin in infants and children scheduled for vitrectomy.

In summary, I agree with the review team that the overall benefits and risks support the approval of BLA 125,422, Jetrea (ocriplasmin) intravitreal injection for treatment of symptomatic vitreomacular adhesion. The product labeling adequately describes the safety and efficacy findings that should be considered in evaluating treatment options for symptomatic vitreomacular adhesions. The approval includes postmarketing studies to gather additional information to evaluate selected product manufacturing issues.

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Edward Cox, MD, MPH  
Director, Office of Antimicrobial Products  
OND/CDER/OMPT/FDA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EDWARD M COX  
10/17/2012