

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125422Orig1s000**

**MICROBIOLOGY REVIEW(S)**



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 18 October, 2012  
**To:** Administrative File, STN 125422/0  
**From:** Reyes Candau-Chacon, PhD., Reviewer, OC/OMPQ/DGMPA/BMAB  
**Through:** Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB  
**Subject:** Addendum to New Biologic License Application (BLA)  
**US License:** 1866  
**Applicant:** ThromboGenics  
**Facilities:** Fujifilm Diosynth Biotechnologies UK Ltd  
Belasis Avenue, Billingham, Cleveland TS23 1LH, UK  
FEI 3007182567  
**Product:** Jetre<sup>TM</sup> (ocriplasmin) Intravitreal Injection  
**Dosage:** Sterile solution for intravitreal injection; 2mL glass vials containing 0.2 mL ocriplasmin at 2.5 mg/mL to be diluted with 0.9% sodium chloride solution for injection at 1:1 ratio prior to injection.  
**Indication:** Treatment of Symptomatic Vitreomacular Adhesion including Macular Hole  
**Due date:** 17 October 2012

The purpose of this addendum is to report the verification of raw test data submitted by (b) (4) to the Agency on (b) (4) in relation to the potential data integrity brought up after FDA inspection (b) (4) is the endotoxin testing facility for release of ocriplasmin bulk drug substance. Endotoxin release test for ocriplasmin drug product is performed at (b) (4)

(b) (4) submitted the following files:

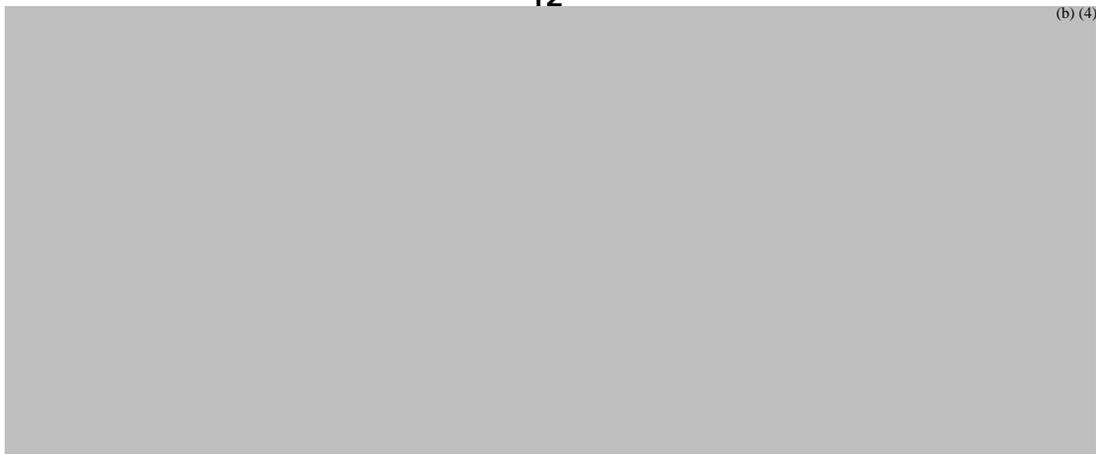
- EL 151-63,
- EL 151-68,
- EL 158-12,
- EL 166-124,
- EL 155-43,
- EL 156-46,
- EL 170-142,
- EL 171-23,
- EL 153-29,

- EL 153-32,
- EL 158-68,
- EL 159-76,
- EL 126-33,
- EL 127-01,
- EL 124-59

The files include raw data for endotoxin validation and revalidation studies, endotoxin robustness studies, endotoxin in-process results and bulk drug substance release for batches B2436-1 to B2436-11. Only reports relevant to data included in the BLA are reviewed here.

File EL 158-12 contains raw data (copies of laboratory notebooks) and validation report of the endotoxin test method included in the BLA. The validation was performed using samples from conformance batches B2436-007, B2436-008, and B2436-009. File 158-12 raw data are identical to the data included in the BLA validation report. A summary of the raw data in EL 158-12 is shown in Table 1.

**Table 1: Summary of endotoxin validation method raw data included in EL 158-12**



(b) (4)

Files EL 158-68 and EL 159-76 include BDS endotoxin release raw data and reports for batches B2436-005 and B2436-006 (EL 158-68) and batches B2436-007, B2436-008, B2436-009 (EL 159-76). All endotoxin results in the files are consistent with the results included in the BLA (b) (4). Endotoxin concentration is expressed in EU/mL in the validation report and as EU/mg in the batch analysis. However, this does not affect endotoxin results (b) (4).

Based on the information reviewed in this addendum I find no discrepancy between raw data submitted by ACC and endotoxin results reported in the BLA. I find no evidence to support concerns regarding data integrity at ACC.

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/s/  
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REYES CANDAU-CHACON  
10/18/2012

PATRICIA F HUGHES TROOST  
10/19/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue,  
Building 51,  
Silver Spring, MD 20993

**Date:** October 02, 2012  
**To:** Administrative File, STN 125422/0  
**From:** Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsement:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** Biological License Application (BLA)  
**US License:** # 1866  
**Applicant:** ThromboGenics Inc.  
**Mfg Facility:** [REDACTED] (b) (4)

**Product:** Jetrea™ (ocriplasmin)  
**Dosage:** Sterile solution for intravitreal administration containing ocriplasmin at a concentration of 2.5mg/mL  
**Indication:** Treatment of Symptomatic vitreomacular adhesion including macular hole  
**Due Date:** October 17, 2012.

**Recommendation for Approvability:** The BLA is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective with the following post-market commitments:

1. Please validate the [REDACTED] (b) (4) with sufficient controls for use with the LAL endotoxin assay using 3 lots of Ocriplasmin Drug substance /Drug product samples. The validation information and data should be submitted as a post market commitment.
2. Please validate yeast and mold recovery in TSA and demonstrate the comparability to the traditional compendial method or requalify the method suitability testing using SDA plates for mold & yeast incubated at 30-35°C for ≤ 5 days as per USP<61> with 3 lots of in process samples. Please provide the information and data of the validation / requalification as a post market commitment.

**SUMMARY:** ThromboGenics submitted a new biologics license application, STN 125422 to license Jetrea® (ocriplasmin). The recombinant protein ocriplasmin is produced by *Pichia pastoris*. Ocriplasmin has a potent proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) and used for the treatment of Symptomatic vitreomacular adhesion including macular hole. Drug substance is manufactured by Fujifilm Diosynth Biotechnologies UK Limited and drug product is formulated, filled and finished at [REDACTED] (b) (4)

The BLA is submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2-Cover letter, and Module 2 and 3. The information request responses submitted on 18 July 2012 in Sequence 0008, on 21 August 2012 in Sequence 0013, on 29 August 2012 in Sequence 0014, on 06 September 2012 in Sequence 0016 and on 02 October 2012 in Sequence 0019 were reviewed.

**ASSESSMENTS:**

Ocriplasmin (previously known as Microplasmin) is a truncated form of human plasmin with retained protease activity. It is a serine protease that selectively cleaves peptide bonds located after a lysine or an arginine residue. The tight binding of the protein components within the macular area of the VRI contribute to VMA and vitreomacular traction, leading to visual impairment and/or macular hole. Ocriplasmin has a potent proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) (e.g. laminin, fibronectin and collagen), dissolving the protein matrix responsible for the abnormal vitreomacular adhesion (VMA). The target indication for ocriplasmin drug product is treatment of symptomatic vitreomacular adhesion including macular hole.

The drug product is a sterile, clear, colorless solution for intravitreal injection which contains 0.5mg ocriplasmin in 0.2mL solution (2.5mg/mL), in (b) (4) (2mL) single use (b) (4) glass vials. The formulation does not contain preservatives. Prior to intravitreal administration, drug product is 1:1 diluted with sodium chloride (0.9% w/v) solution for injection. The recommended dose is 0.125mg (125µg) corresponding to 0.1mL of the diluted solution.

FDA has granted a Priority Review status for this BLA according to FD&C Act, Section 506(a) based on the drug demonstrating the potential to address an unmet medical need where no nonsurgical therapies are available.

**DRUG SUBSTANCE**

The recombinant protein ocriplasmin is produced by *Pichia pastoris* in the form of the precursor microplasminogen, (b) (4)

(b) (4)

The drug substance section of this submission has been reviewed by Dr. Maria Candauchacon.

**3.2.P DRUG PRODUCT**

Ocriplasmin drug product is manufactured by (b) (4)

(b) (4)

Prior to intravitreal administration, ocriplasmin drug product is diluted using an equal volume of a 0.9% w/v sodium chloride solution.

**3.2.P.1 Description and Composition of the Drug Product**

Ocriplasmin drug product is a clear, sterile solution for intravitreal administration containing ocriplasmin at a concentration of 2.5mg/mL and is diluted with an equal volume of 0.9% (w/v) sodium chloride prior to use.

Ocriplasmin drug product is filled in (b) (4) USP/Ph. Eur. glass vials with a 0.2mL fill volume. The vials are closed with (b) (4) (b) (4) rubber stoppers. The stoppers are capped with an aluminium crimp seal equipped with a (b) (4) flip-off cap. The composition of ocriplasmin drug product is presented in the following table:

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**Environmental Assessment**

According to the firm, ocriplasmin (2.5 mg/mL) meets the criteria for categorical exclusion under 21 CFR 25.31(c) for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The active drug substance ocriplasmin is a recombinant version of a naturally occurring human enzyme, which would have the same metabolites or degradation products as the non-recombinant version. In addition, the quantity of ocriplasmin administered generally to a selected population is very low (125 µg). The estimated concentration or distribution of the substance itself and its metabolites and degradation products would be significantly below 1 part per billion at the point of entry into the aquatic environment.

**CGMP Status**

(b) (4)  
This general CGMP surveillance inspection also covered BLA STN 125422 with (b) (4) and (b) (4) profiles. The inspection is classified as VAI. A final TB EER with the compliance status of all the facilities listed in the BLA from DGMPA/NDMAB is pending.

**Conclusion**

- I The drug product section of this BLA was reviewed from sterility assurance perspective and is recommended for approval with the following post market commitments:
1. Please validate the (b) (4) with sufficient controls for use with the LAL endotoxin assay using 3 lots of Ocriplasmin Drug substance /Drug product samples. The validation information and data should be submitted as a post market commitment.
  2. Please validate yeast and mold recovery in TSA and demonstrate the comparability to the traditional compendial method or requalify the method suitability testing using SDA plates for mold & yeast incubated at 30-35°C for ≤ 5 days as per USP<61> with 3 lots of in process samples. Please provide the information and data of the validation/requalification as a PMC.
- II The remaining drug product section of the BLA should be reviewed by the OBP reviewer.
- III The inspection of the drug product manufacturing site, (b) (4) A CGMP surveillance inspection of this facility conducted on (b) (4) also covered BLA STN 125422 with (b) (4) and (b) (4) profiles. The inspection is classified as VAI. A final TB EER with the compliance status of all the facilities listed in the BLA from DGMPA/NDMAB is pending.

CC: Building 51, Hughes  
Building 51, Narasimhan  
Building 22, Smith

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/s/  
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LAKSHMI RANI NARASIMHAN  
10/02/2012

PATRICIA F HUGHES TROOST  
10/02/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 01 October, 2012  
**To:** Administrative File, STN 125422/0  
**From:** Reyes Candau-Chacon, PhD., Reviewer, OC/OMPQ/DGMPA/BMAB  
**Through:** Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB  
**Subject:** New Biologic License Application (BLA)  
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**Indication:** Treatment of Symptomatic Vitreomacular Adhesion including Macular Hole  
**Due date:** 17 October 2012

**Recommendation for Approvability:** The drug substance part of this application is recommended for approval from microbiology product quality perspective.

1. Submit new limits for bioburden (action limit (b)(4) and endotoxin (action limit (b)(4); alert limit (b)(4)) in (b)(4) of (b)(4) as a CBE-0 by the end of 03/2013.
2. Qualify bioburden and endotoxin methods for (b)(4) and (b)(4) and establish bioburden and endotoxin specifications based on an assessment of risk to ocriplasmin product quality. The outcome of the risk assessment and the bioburden and endotoxin specifications will be submitted as a CBE-0 by the end of 03/2013.
3. Investigate the use of (b)(4) for endotoxin measurements of in-process samples (b)(4) and revise the endotoxin methods accordingly. Any changes to the in-process endotoxin methods will be submitted as a CBE-0 by the end of 03/2013.
4. Validate the efficacy of the (b)(4) and submit a report as a CBE-0 by the end of 03/2013.

5. Evaluate the effects of freezing on endotoxin recovery from ocriplasmin drug substance. These studies will include [REDACTED] (b) (4) as appropriate. Any changes to the in-process endotoxin methods will be submitted as a CBE-0 by the end of 03/2013.
6. Qualify the bioburden method for [REDACTED] (b) (4) and submit a report as a CBE-0 by the end of 03/2013.

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**Review Summary**

ThromboGenics has submitted BLA 125422 to license ocriplasmin drug substance and drug product manufacturing processes. Ocriplasmin is a recombinant truncated form of human plasmin for the treatment of vitreomacular adhesion. The bulk drug substance (DS) is manufactured at Fujifilm Diosynth Biotechnologies UK Ltd. The drug product is manufactured at [REDACTED] (b) (4)

BLA 125422 was submitted in eCTD format on 17-April-2012. Amendments under sequences 0003, 0010, and 0019 were submitted on 15-June-2012, 03-August-2012, and 28-September-2012 to address information requested by the FDA. This review contains the assessment of the manufacturing process of ocriplasmin bulk drug substance from microbiology product quality perspective. For review of drug product aspects of the application, please see review by Dr. Lakshmi Narasimhan.

**Review Narrative**

**S DRUG SUBSTANCE**

**S.1 General Information**

Ocriplasmin is a 27.2kDa, truncated form of human plasmin with retained protease activity produced by *Pichia pastoris*. [REDACTED] (b) (4)

[REDACTED] (b) (4)

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