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RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

CHEMISTRY REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: October 17, 2012

Applicant Name: ThromboGenics
U.S. License #: 1866
STN(s): 125422/0
Product(s): Jetrea™ (ocriplasmin) Intravitreal Injection

Short summary of application: BLA to request approval of a Jetrea™ (ocriplasmin) Intravitreal Injection

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Fujifilm Diosynth Biotechnologies UK Ltd
Address: Belasis Avenue, Billingham, Cleveland TS23 1LH, UK
FEI: 3007182567

Short summary of manufacturing activities performed: Manufacturing, labeling, release testing, monitoring storage of WCB, storage of MCB

Inspected by CDER OMPQ from (b) (4) and classified VAI. This inspection covered DS manufacturing operations and found the TRP profile updated and acceptable. This inspection covered manufacturing operations for this BLA.

Firm Name:
Address:
FEI:

(b) (4)

Short summary of manufacturing activities performed: Stability testing of DS and DP, release testing (SDS page, potency)

This site was inspected by IOG from (b) (4) and initially classified OAI. This CGMP / PAI inspection provided coverage of the firm's testing operations in support of this BLA. The inspection noted deficiencies in the execution of the stability protocol used to support the BLA. Specifically, the firm did not document and could not confirm that stability samples at the (b) (4) condition were stored (b) (4). As the firm's response to inspectional deviations has not yet been received by the Agency, DIDQ is unable to provide an acceptable compliance recommendation in support of this BLA. DGMPA has weighed the significance of the finding

related to the subject product and finds that the observation does not pose a significant risk to the stability program because the product is stored at -20°C. . Therefore DGMPA finds this site acceptable for the purposes of this BLA.

Firm Name: [REDACTED] (b) (4)
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: Storage of Master and Working Cell Bank

Inspected by [REDACTED] (b) (4) from [REDACTED] (b) (4) and classified NAI. Cell banking operations were covered and are acceptable.

Firm Name: [REDACTED] (b) (4)
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: DS release testing for Western Blot, [REDACTED] (b) (4)

Inspected by IOG from [REDACTED] (b) (4) and classified NAI. This biotech CGMP inspection covered testing operations and found the CTL profile updated and acceptable.

Firm Name: [REDACTED] (b) (4)
Address: [REDACTED]
DUNS: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: DS release testing for endotoxin

This facility was inspected by IOG from [REDACTED] (b) (4) and initially classified VAI for general CGMP compliance. This inspection also provided pre-approval coverage for operations in support of this BLA. During the course of the inspection, the firm withheld all data and records that were required to assess CGMP compliance of commercial drug substance endotoxin testing in support of this BLA. The investigator was led to believe by representatives of this firm that [REDACTED] (b) (4) was not contracted to perform commercial drug substance manufacturing operations in support of this BLA. After the inspection closed and these findings were reported to CDER, DIDQ and DGMPA attempted to clarify the discrepancy between inspectional findings and BLA commitments with Thrombogenics, [REDACTED] (b) (4) [REDACTED] (b) (4). During a teleconference, [REDACTED] (b) (4) stated that they had withheld pertinent information from the investigator for fear of breaching confidentiality, despite being aware that the purpose of the investigator's inspection was to verify that operations in support of the BLA were compliant to CGMP. IOG and DIDQ have recommended withholding approval due to the refusal of the firm to provide information during the pre-approval inspection and the inability to verify readiness for commercial manufacturing operations, conformance to application commitments, and integrity of supporting data. In evaluating the case, DGMPA/NDMAB has determined the following:

- A Post-Marketing Commitment (PMC) is necessary to support the drug substance endotoxin testing based on the withheld information for the inspection. Information provided on [REDACTED] (b) (4) indicates that Thrombogenics [REDACTED] (b) (4)

(b) (4)

- Based on request from DGMPA/NDMAB, Thrombogenics had this facility submit information that would typically be evaluated during inspection (b) (4). The request was for the method validation report, data supporting the method validation, and the data for all batches that were sent to (b) (4) for release testing of endotoxin. DGMPA reviewed this additional information within 2 hours regarding method validation and testing operations made available by the firm after the inspection (provided (b) (4)). After reviewing this information, DGMPA does not find significant concerns that warrant withholding approval of this BLA.

In summary, DGMPA finds this site acceptable for the purposes of this BLA based on the acceptance of the PMC.

Firm Name:

(b) (4)

Address:

FEI:

Short summary of manufacturing activities performed: DS release testing (b) (4). DS release and stability testing for low pH SE-HPLC and low pH cation exchange-HPLC, and enzyme kinetic properties (Km + keat) and cation exchange-HPLC

Inspected by IOG from (b) (4) and classified NAI. This CGMP inspection covered testing operations and found the CTL profile updated and acceptable.

(b) (4)

FEI Number:

(b) (4)

Short summary of manufacturing activities performed: drug product manufacturer

Inspected by IOG from (b) (4) and classified VAI. This CGMP / PAI provided coverage for operations in support of BLA 125422. The PAI found that the firm's original records showed data integrity and conformance to the BLA, and that the facility is ready and capable to manufacture the drug product in conformance with CGMPs. This site is acceptable for this BLA.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this BLA.

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The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to

further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAHESH R RAMANADHAM
10/17/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Jee Chung, Ph.D.
Kathy Lee, M.S.
Division of Therapeutic Proteins

Through: Susan Kirshner, Ph.D.
Division of Therapeutic Proteins

BLA Number: 125422
Product: JETREA (ocriplasmin)
Sponsor: Thrombogenics Inc.

Date of Review: September 13, 2012
Due Date of CDTL Memo: October 15, 2012

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins , Office of Biotechnology Products, OPS, CDER, recommends approval of BLA 125422 for JETREA (ocriplasmin) manufactured by Thrombogenics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of JETREA (ocriplasmin) is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert). There are several CMC issues that the sponsor should address that are not required for approval of this application (see draft PMC's listed below). For final PMC language see Approval Letter.

II. APPROVAL LETTER INFORMATION

Drug Substance (DS) Manufacturer:
Fujifilm Diosynth Biotechnologies UK Ltd
Belasis Avenue,
Billingham, Cleveland TS23 1LH (UK)
Facility Establishment Identifier: 3007182567

(b) (4)

USAN Name: Ocriplasmin
Marketed Name: JETREA

The recommended storage condition for (b) (4) drug product is -20°C (b) (4) Ocriplasmin drug substance is stable when stored at (b) (4) (b) (4) and the drug product is stable when stored at -20°C (b) (4) for up to 18 months.

(b) (4)

The sponsor submitted protocols for the establishment of new master and working cell banks. The protocols are acceptable.

A protocol for the extension of drug product shelf life was submitted. The protocol is acceptable.

III. DRAFT POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

Note the final PMC language will be in the approval letter including commitments dates.

1. To perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood more than one patient could be dosed from the same single use vial due to excess reconstituted drug product remaining in the vial after the initial dosing.

The final study report will be submitted in 03/13.

2. To revise the acceptance criteria for the drug substance and drug product release and stability specifications for low pH CEX-HPLC, RP-HPLC, and low pH SEC-HPLC to include “No new peaks above the limit of quantitation” and for non-reduced SDS-PAGE “No new bands greater than the limit of quantitation.”

Interim Report Submission: 12/12

Final Report Submission: 04/13

3. To establish an upper limit for the acceptance criterion for (b) (4) potency assay or provide data to justify why this is not necessary.

The final study report and, if required, revised specification will be submitted in 12/12.

4. To evaluate and revise, as needed, the acceptance criteria for the all drug substance release specifications based on data from at least thirty lots of each.

The final study report and, if required, revised specification will be submitted in 12/15

5. To evaluate and revise, as needed, the acceptance criteria for the all drug product release specifications based on data from at least thirty lots of each.

The final study report and, if required, revised specification will be submitted in 12/17

6. To revise the system suitability criteria for RP-HPLC, and drug substance and drug product release and stability methods to ensure adequate column performance.

The updated system suitability criteria will be submitted in 03/13.

7. To revise the system suitability criteria for the SDS-PAGE the drug substance and drug product release and stability methods to establish an acceptance criterion for the (b) (4)

The updated system suitability criteria will be submitted in 03/13.

8. To establish the limit of quantitation for the RP-HPLC and SDS-PAGE methods.

The validation reports will be submitted in 3/13.

9. To provide data to support alternative sampling methodology for sub-visible particles testing using USP <789> monograph.

The final study report will be submitted in 10/12.

10. Develop release and stability method(s) to detect all types of aggregates observed (b) (4) in your drug product.

The final study report will be submitted in 08/13.

11. Provide the results of the study conducted to evaluate the discrepancy in copy number results between the (b) (4) assay and the (b) (4) assay.

The final study report will be submitted in 03/13.

12. To determine the approximate percentage (b) (4) by 2D SDS-PAGE or a similarly sensitive and discriminating assay.

The final study report will be submitted in 06/13.

13. To submit a reference (standard) material qualification protocol for new primary and secondary reference materials which contains characterization testing and more stringent acceptance criteria for release assays performed as part of the qualification of the new reference materials.

The new protocol will be submitted in 03/13.

14. To conduct an extractable study for the (b) (4) rubber stoppers used for the drug product container closure (b) (4). This information should be used in the risk assessment conducted for drug product final container closure system leachable study.

The final study report will be submitted in 12/12

15. To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product in the final container closure system at the end shelf-life.

The final study report will be submitted in 12/13.

16. To evaluate drug substance for the presence of yeast cell wall components (i.e. chitin, mannans, and β -glucans). Provide a risk assessment of the potential impact these product related impurities may have on the quality, safety and efficacy of ocriplasmin and propose an appropriate control strategy.

The final study report will be submitted in 03/13.

17. To conduct a drug product stability study demonstrating that drug product stored at -70°C for 120 days followed by storage at -20°C up to the expiry (18 months) does not adversely impact product quality.

The final study report will by submitted in 12/13.

Note, the primary review contains several suggested PMCs and two PMRs which were removed or modified. The initial PMR/PMC will be listed first in bold and an explanation of why the PMC is not required or why it was modified.

Removed Post Marketing Requirements

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

(b) (4)

The language of this PMC was change to be clearer about our requirements.

IV. EXECUTIVE SUMMARY

A. Description of Ocriplasmin

Ocriplasmin is a recombinant 27.2 kDa protein that belongs to the serine protease family. Serine proteases are known to selectively cleave the peptide bonds at the carboxyl termini of arginine or lysine residues in target proteins and peptides. Ocriplasmin is expressed in *Pichia pastoris* as an inactive microplasminogen (zymogen). (b) (4)

(b) (4) Ocriplasmin is purified to (w) (4) % purity, as detected by RP-HPLC method.

The final drug product is a sterile, clear and colorless solution containing 0.5mg ocriplasmin in 0.2mL solution in 2 mL single use (b) (4) glass vials, stored frozen at -20 (b) (4) °C. Prior to use, the vial is thawed and diluted with 0.9%(w/v) sodium chloride solution at 1:1 ratio. The recommended dose for the current indication is 125µg, which corresponds to 0.1mL of the diluted solution and is administered by intravitreal injection.

The sponsor claims categorical exclusion under 21 CFR 25.31(c), which provides exclusion for an action on an application for a marketing approval of a biological product

¹ G.E. Gasparich "Spiroplasmas and phytoplasmas: Microbes associated with plant host." Biologicals 38 (2010) 193-203

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. Ocriplasmin is a recombinant version of a truncated human plasmin, which would have the same metabolites or degradation products as the non-recombinant version. Therefore, ocriplasmin metabolites and degradation products would not significantly alter the environment.

B. Clinical Trial Information

Ocriplasmin is indicated for the treatment of symptomatic vitreomacular adhesion (VMA). The goal of therapy for symptomatic VMA including macular hole is to relieve tractional effects on the macula with subsequent functional, *i.e.* visual improvement. Ocriplasmin is administered through intravitreal injection.

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. In addition, three Phase 2 studies were conducted in support of the symptomatic VMA indication.

C. Stability

The long term storage condition for the ocriplasmin (b) (4) DP is at -20°C. The BLA submission contained real time stability data (b) (4) 12 (primary study) and 18 (supportive study) months for DP. The stability data supports an expiry of (b) (4) 18 months for DP.

The stability data at -70°C, -20°C, 5°C, and 25°C were provided for both the DS and DP. The latter two temperatures are the accelerated and stressed storage temperatures. (b) (4)

(b) (4)
The stability indicating assays are SDS-PAGE reduced and non-reduced, RP-HPLC, and CEX-HPLC methods. (b) (4)

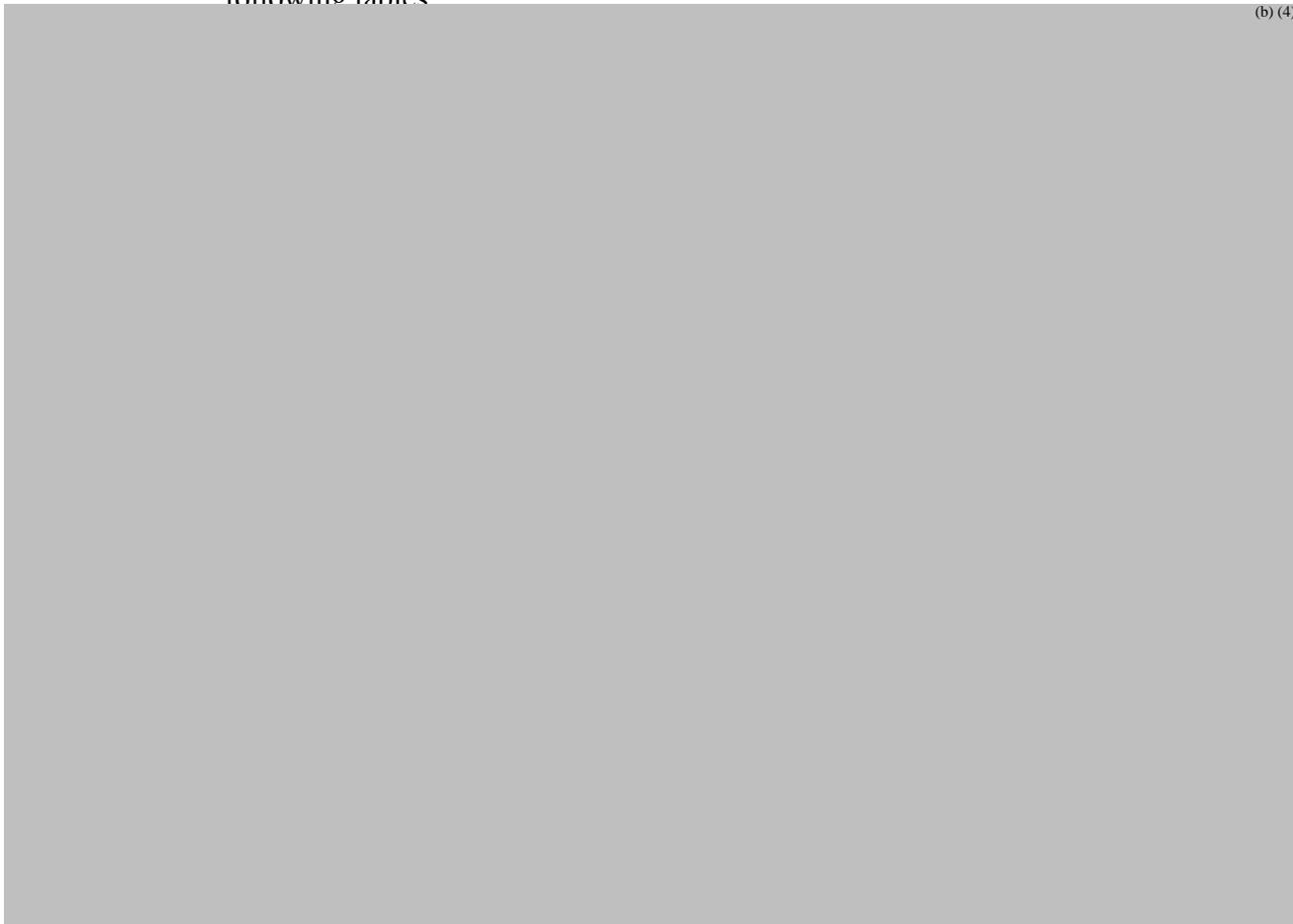
Photostability studies were conducted for both the DS and DP in their final container closure systems. (b) (4)

(b) (4) However, the DP will be stored within a secondary container to prevent exposure to light and the product label states to protect from light.

D. Complexity

- **Critical Quality Attributes**

The critical quality attributes and product-related variants are listed in the following tables:



(b) (4)

Table 1: Product-Related Impurities and Product-Related Substance in Ocriplasmin Drug Substance

(b) (4)

See Appendix 1 for a list of DS and DP release and stability specifications. Some of the specification acceptance criteria are broad. However, there is no safety concern about having wider acceptance criteria at this time (b) (4)

The clinical studies were conducted using drug product (b) (4) See section H below for more information on comparability between the three processes. A PMC was created for the sponsor to assess all DS and DP specification after 30 lots are produced.

E. Homology to Other Products

Ocriplasmin is a truncated version of human plasmin.

F. Mechanism of Action

The target indication for ocriplasmin is treatment of vitreomacular adhesion (VMA) including macular hole. VMA results from abnormally tight association of vitreal protein components, including fibronectin and laminin, at the vitreoretinal interface (VRI) and subsequent age-dependent traction leading to macular hole development. Ocriplasmin is a truncated version of human plasmin, It has serine protease activity and is 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 helps in dissolution of the matrix proteins at the abnormal VRI focal points thereby resolving or reducing the complications associated with VMA. Using synthetic peptide S-2403 as substrate, at physiological pH (7.4) and 37°C, Ocriplasmin’s proteolytic activity has been

determined [REDACTED] (b) (4)

Since Ocriplasmin's primary mechanism of action (MoA) is proteolytic cleavage of matrix proteins at vitreoretinal interface in patients with VMA, the appropriate bioassay for release and/or characterization in this case would be to measure its proteolytic activity. Accordingly, Ocriplasmin's potency is determined by measuring enzymatic kinetics (Km and Kcat values), using a chromogenic substrate called, *L*-pyroglutamyl-*L*-phenylalanyl-*L*-lysine-*p*-nitroaniline hydrochloride (Glp-Phe-Lys-pNA.HCl, or S- 2403).

G. Manufacturing Process

Recombinant ocriplasmin is produced in a methylotrophic yeast (*Pichia pastoris*) production system [REDACTED] (b) (4). Manufacture of ocriplasmin drug substance is performed in accordance with cGMP by Fujifilm Diosynth Biotechnologies UK Limited (Fujifilm) [REDACTED] (b) (4). The ocriplasmin drug substance manufacturing process is comprised of [REDACTED] (b) (4) stages, summarized in the flow diagram presented in Figure 1 below.

Figure 1: Overview of Ocriclasmin Drug Substance Manufacture

(b) (4)



(b) (4)



H. Comparability

The ocriclasmin drug substance was manufactured using (b) (4) manufacturing processes during the course of development. Non-clinical, Phase 1 and Phase 2 studies were conducted using ocriclasmin drug substance (b) (4)





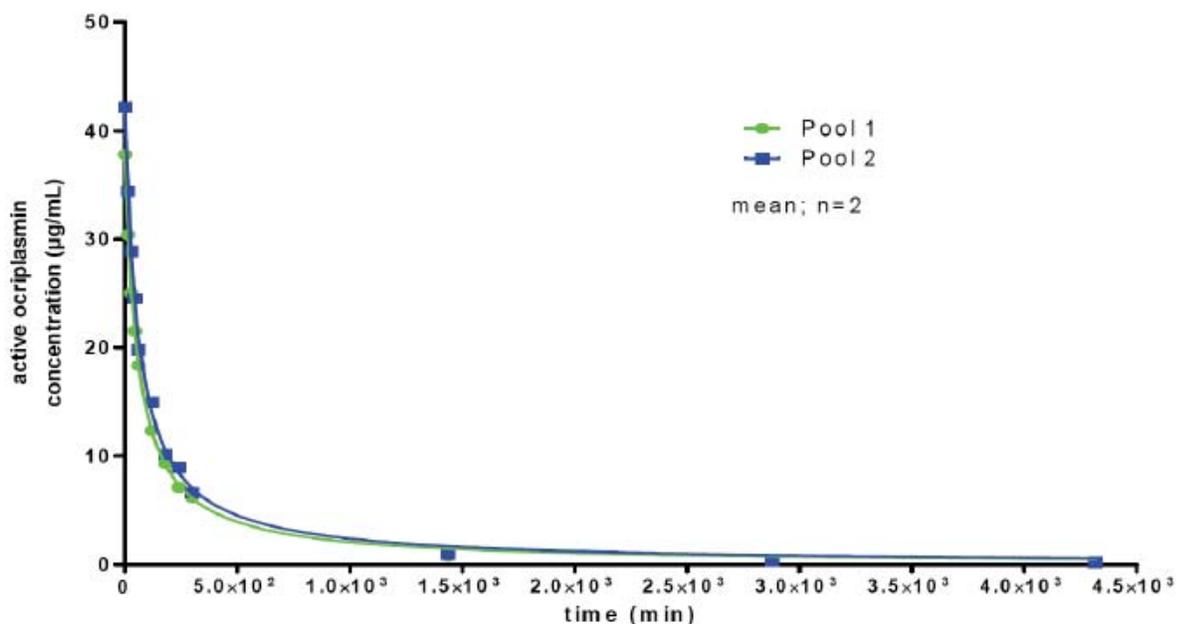
I. Immunogenicity

Immunogenicity for this product has not been evaluated. This product is injected directly into the eye and will be indicated for a one time dose only.

Below is a summary of a study Thrombogenics performed to assess the enzymatic activity of ocriplasmin in human vitreous fluid. This data shows that ocriplasmin is generally cleared within 4 hours of dosing.

Per the Clinical pharmacology review; “the PK properties of a single 125µg IVT dose of ocriplasmin were evaluated when administered at different time points prior to planned primary pars plana vitrectomy in patients with eye disease. All patients (n=16) had IVT ocriplasmin activity levels above LLOQ between 0.5 and 4 hours post-dose, and 50% of patients (2/4) displayed IVT ocriplasmin activity levels below LLOQ at 24+/-2 hours post-dose.” See table below.

Figure 6: Inactivation of Ocriplasmin in Pooled Human Vitreous Fluid (3mL) Following the Addition of 125 µg Ocriplasmin and Incubation at +37°C



Because the product will only be used once via intraocular injection, requiring an immunogenicity safety study at this point in development is not necessary. However if the Sponsor ever performs additional safety or efficacy studies with this product immunogenicity should be evaluated.

APPENDIX 1

The current and proposed DS release and stability specifications are shown below:

Table 1: Current and Proposed Ocriplasmin Drug Substance Specifications

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
General Properties:				
Appearance	Visual Inspection (AM0770)	turbidity, coloration and particulate matter	clear, colourless solution, practically free from visible particulate matter	clear, colourless solution, practically free from visible particulate matter
pH	Potentiometric USP <791> and Ph.Eur. 2.2.3 (AM0001)	pH	pH 2.8 to pH 3.4	pH 2.8 to pH 3.4
Osmolality	Freezing Point Depression (AM0484)	osmolality	report result	(b) (4)
Identity:				
Size and Epitope	Western Blot (PIC09-053)	recognise bands using specific antibody	comparable to reference standard profile	(b) (4)
Isoelectric Point	IEF (AM0705)	pH at isoelectric point	comparable to reference standard profile	(b) (4)

SUMMARY BLA125422 USAN --Ocriplasmin

Table 1: Current and Proposed Ocriplasmin Drug Substance Specifications (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Purity and Impurities:				
Molecular Size Variants (Reducing and Non-reducing Conditions)	Reduced SDS-PAGE (AM0710) Non-reduced SDS-PAGE (AM0710)	(b) (4)		
Hydrophobic Molecular Variants	RP-HPLC (AM0704)	(b) (4)		
Molecular Charge Variants	CEX-HPLC (pH5.5)* (AM0702)	(b) (4)		

SUMMARY BLA125422 USAN --Ocriplasmin

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
	Low pH CEX- HPLC ^b (SOPQA- MICROPLASM -R-001)	(b) (4)	(b) (4)	(b) (4)
Molecular Size Variants	SE-HPLC (pH 7.4) ^c (AM0698)	Ocriplasmin peak (b) (4)	(b) (4)	(b) (4)

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Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
	Low pH SE-HPLC ^d (SOPQA-MICROPLASM-R-002)	(b) (4)	(b) (4)	(b) (4)

Table 1: Current and Proposed Ocriplasmin Drug Substance Specifications (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Process Related Impurities:				
(b) (4)	Process specific ELISA method (PIC09-011)	quantity	(b) (4)	
	qPCR method (SOPQA-Microplasm-ADN-001)	quantity		
	ELISA method (PIC09-048)	quantity		
	UV 610nm (AM0689)	quantity		
Quantity:				
Protein Concentration	UV 280nm (AM0608)	quantity		
Potency:				
Potency ^e	Enzymatic Activity (AM0634)	proteolytic activity	(b) (4)	
Enzyme Kinetic	Enzyme activity	Km		
Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
		k _{cat}	(b) (4)	

SUMMARY BLA125422 USAN --Ocriplasmin

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
General Properties				
Appearance	visual inspection (Ph.Eur. 2.2.2 and Ph.Eur. 2.2.1 - ATP957)	turbidity, coloration and particulate matter	clear, colourless solution practically free from visible particulate matter	colour less than or equivalent to Ph.Eur. B ₉ reference solution, clarity less than or equivalent to Ph.Eur. reference suspension I, sample solution is practically free from visible particulate matter
pH	potentiometric (USP<791> and Ph.Eur. 2.2.3 - ATP164)	pH	pH 2.8 to pH 3.4	pH 2.8 to pH 3.4
Osmolality	freezing point depression (USP<785> and Ph.Eur. 2.2.35 - ATP841)	osmolality	report result	(b) (4)
Sub-visible Particles (particles/ container)*	light obscuration test (ATP838)	particle count		(b) (4)
Sub-visible Particles (particles/mL) ^b	membrane microscopy test (SOPQA-OCRIPLAS-MIN-MP-001)	particle count		

SUMMARY BLA125422 USAN --Ocriplasmin

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Identity				
Size and Epitope	Western Blot (PIC09-053)	immunological specificity for ocriplasmin	comparable to reference standard profile	(b) (4)
Isoelectric Point	IEF (ATP953)	pH at isoelectric point	comparable to reference standard profile	(b) (4)
Purity and Impurities				
Molecular Size Variants (Reduced and Non-reduced Conditions)	reduced SDS-PAGE (AM0710) non-reduced SDS-PAGE (AM0710)	(b) (4)	(b) (4)	(b) (4)

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Hydrophobic Molecular Variants	RP-HPLC (AM0704)	(b) (4)	(b) (4)	(b) (4)
Molecular Charge Variants	CEX-HPLC (pH 5.5) ^c (AM0702)	(b) (4)	(b) (4)	(b) (4)
	Low pH CEX-HPLC (pH 4.0) ^e (SOPQA-MICROPLAS M-R-001)	(b) (4)	(b) (4)	(b) (4)

SUMMARY BLA125422 USAN --Ocriplasmin

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Molecular Size Variants	SE-HPLC (pH 7.4) ^f (AM0698)		(b) (4)	(b) (4)
Molecular Size Variants	low pH SE-HPLC (pH 3.1) ^g (SOPQA-MICROPLAS M-R-002)			(b) (4)
Quantity				
Protein Concentration	UV 280nm (ATP655)	quantity		(b) (4)
Potency				
Potency	enzymatic activity ^h (AM0634)	proteolytic activity		
Enzyme Kinetic Properties ⁱ	enzyme activity (SOPQA-MicroplasmK m-A-001)	K _m		
		k _{cat}		
Other Quality Characteristics				
Uniformity of Dosage Units	quantity (USP<905> and Ph.Eur. 2.9.40 - ATP954)	quantity		

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Endotoxin	turbidity of LAL reagent (USP<85> and Ph.Eur. 2.6.14 - M103-R70-2.2)	endotoxin quantity		(b) (4)
Sterility	membrane filtration (USP<71> and Ph.Eur. 2.6.1 - M103-R70-2.1)	sterility	absence of growth	absence of growth
Container closure integrity	Blue dye ingress test (ATP 900)	Blue dye ingress	N/A ^d	No ingress

^a Method used historically for batch release and stability testing. Superseded by membrane microscopy sub-visible particles method

^b Replaces the light obscuration sub-visible particles method

^c Method used historically for batch release and stability testing. Superseded by low pH CEX-HPLC (pH 4.0) method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the current acceptance criteria will be used

^d N/A = not applicable as method has been superseded or only recently introduced

^e Replaces the CEX-HPLC (pH 5.5) method for batch release and stability testing

^f Method used historically for batch release and stability testing. Superseded by low pH SE-HPLC (pH 3.1) method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the current acceptance criteria will be used

^g Replaces the SE-HPLC (pH 7.4) method for batch release and stability testing

^h Method used historically for batch release and stability testing. Superseded by enzyme kinetic properties km/k_{cat} method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the acceptance criterion will be between $37\mu M/min/mg$ and $59\mu M/min/mg$

ⁱ Replaces the potency method AM0634 for batch release and stability testing

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/s/

SUSAN L KIRSHNER on behalf of MARY K W LEE
10/15/2012

SUSAN L KIRSHNER
10/15/2012

BLA STN 125422

**Product USAN name
Ocriplasmin**

**License Holder
Thrombogenics Inc.**

**Reviewers: Ramesh Potla, Richard Ledwidge, Leslie Rivera Rosado
Maria Teresa Gutierrez-Lugo, Nikolay Spiridonov, Frederick Mills,
and Jee Chung**

LC/TL Reviewer: Jee Chung and Kathy Lee

Division of Therapeutic Proteins

OBP CMC Review Data Sheet

1. **BLA#:** STN 125422
2. **REVIEW DATE:** 8/23/12
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Jennifer Harris
Pharm/Tox: Maria Rivera
Product Quality Team: Ramesh Potla, Leslie Rivera Rosado, Richard Ledwidge, Maria Teresa Gutierrez-Lugo, Nikolay Spiridonov, Fred Mills, and Jee Chung
BMT or Facilities: Maria Candauchacon and Lakshmi Narasimhan
Clinical Pharmacology: Yoriko Harigaya
Statistics: Yunfan Deng
OBP Labeling: Kimberly Rains
RPM: Jacquelyn Smith

4. **MAJOR GRMP DEADLINES**

- Filing Meeting:**
- Mid-Cycle Meeting:** July 19, 2012
- Wrap-Up Meeting:** September 24, 2012
- Primary Review Due:** September 19, 2012
- Secondary Review Due:** September 26, 2012
- CDTL Memo Due:** October 3, 2012
- PDUFA Action Date:** October 17, 2012

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	September 30, 2011
Teleconference 1	
Information Request #1	June 8, 2012
Information Request #2	74-Day Letter sent June 27, 2012
Information Request #3	August 31, 2012
Information Request #4	September 5, 2012

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125422/0	April 17, 2012	
STN 125422/11 (response to IR #1)	August 21, 2012	Yes
STN 125422/8 (response to IR #2)	July 18, 2012	Yes
STN 125422/# (response to IR #3 and #4)	September 10, 2012	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Jetrea
- b. Trade Name: Jetrea
- c. Non-Proprietary/USAN: Ocriplasmin
- d. CAS name: 1048016-09-6
- e. Common name:
- f. INN Name: Ocriplasmin
- g. Compendial Name:
- h. OBP systematic name:
- i. Other Names:

8. PHARMACOLOGICAL CATEGORY:

No pharmacological class has been established for this product.

9. DOSAGE FORM:

Liquid

10. STRENGTH/POTENCY:

- (i) The concentration/strength of the Drug Product: 2.5 mg/ml
- (ii) Type of potency assay (s): Enzyme Kinetic Assay (Km and kcat)

11. ROUTE OF ADMINISTRATION:

Intravitreal

12. REFERENCED MASTER FILES:

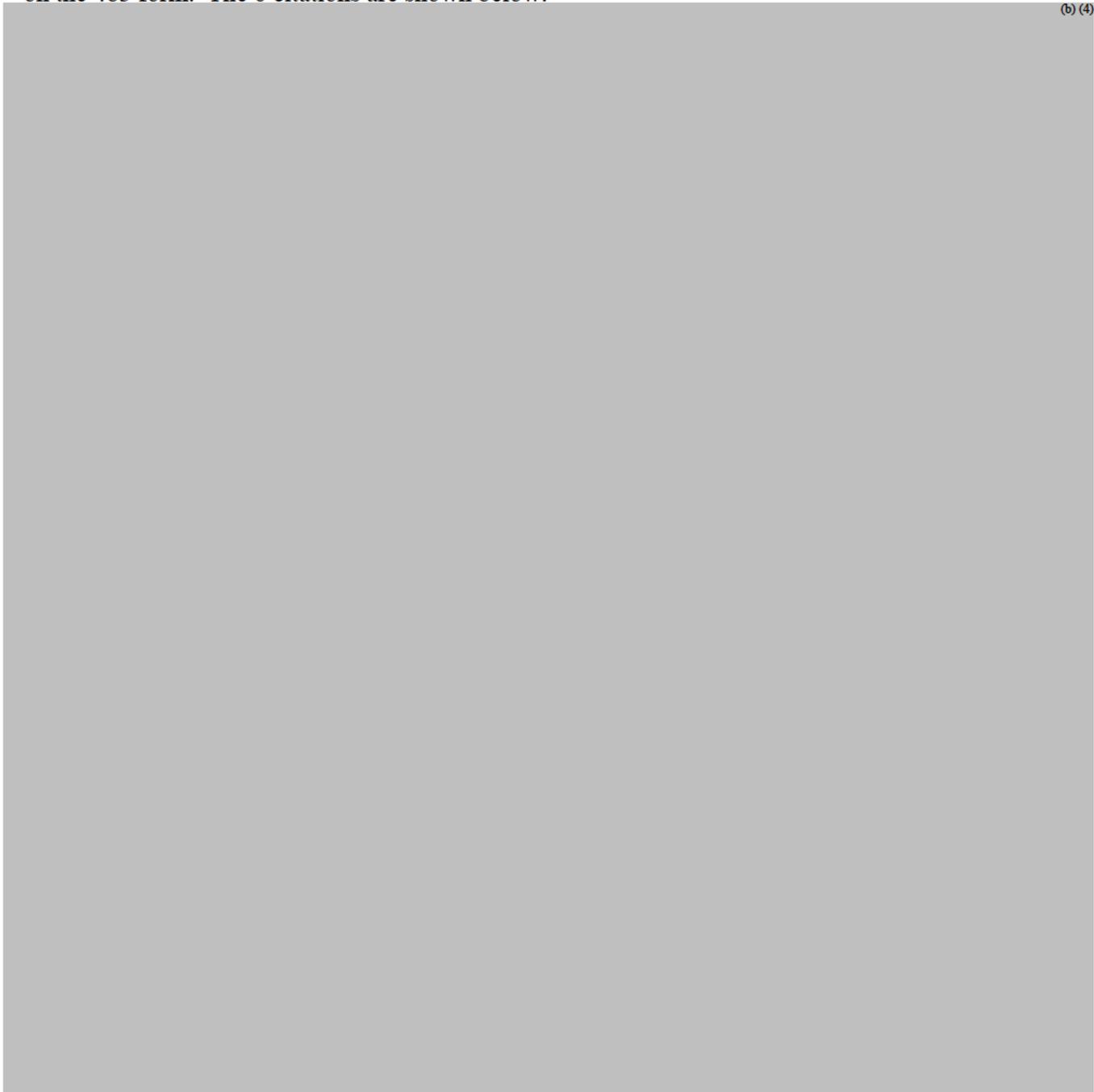
DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	(b) (4)		No review required as all the relevant information related to compatibility with the product was in the BLA.
(b) (4)	(b) (4)	(b) (4)		No review required as all the relevant information related to

				compatibility with the product was in the BLA
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13. INSPECTIONAL ACTIVITIES

Drug substance manufacturing facility inspection occurred June 11-20, 2012. The inspection team consisted of Mary E. Farbman and Reyes Candau-Chacon. A total of 6 issues were cited on the 483 form. The 6 citations are shown below:

(b) (4)



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(CCI/TS) immediately
following this page

14. CONSULTS REQUESTED BY OBP

None.

15. QUALITY BY DESIGN ELEMENTS

None.

16. PRECEDENTS

None.

17. ADMINISTRATIVE

Include in the Signature block in DARRTS all primary review team members and secondary and tertiary team leads.

In the CC Block in DARRTS include the following people: Clinical Division BLA RPM, Deputy Director, DTP, all members of the review team.

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/s/

RAMESH B POTLA
09/19/2012

NIKOLAY A SPIRIDONOV
09/19/2012

RICHARD LEDWIDGE
09/20/2012

FREDERICK C MILLS
09/20/2012

MARIA T GUTIERREZ LUGO
09/20/2012

LESLIE A RIVERA ROSADO
09/20/2012

MARY K W LEE
09/20/2012

MARY K W LEE on behalf of JEE Y CHUNG
09/20/2012