

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761108Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761108
Review Number: 1
Review Date: December 19, 2018

Drug Name/Dosage Form	Ultomiris (ravulizumab-cwvz)
Strength/Potency	300mg/30 mL (10 mg/mL)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Paroxysmal nocturnal hemoglobinuria (PNH)
Applicant/Sponsor	Alexion Pharmaceuticals, Inc.

Product Overview

Ravulizumab-cwvz is a humanized IgG2/4 monoclonal antibody which is manufactured in mammalian CHO cells. Ravulizumab-cwvz binds to C5 and prevents activation of the complement cascade. Eculizumab was approved in 2007 for the treatment of Paroxysmal nocturnal hemoglobinuria (PNH) via the same mechanism of action (binding to C5). Ravulizumab and Eculizumab have the same sequence, except for four point mutations that were introduced to extend the half-life which results in less frequent dosing. Ravulizumab maintenance dosing occurs once every 8 weeks, whereas Eculizumab maintenance dosing is once every 2 weeks. Ravulizumab-cwvz drug product is clear to translucent, slight whitish color solution that is supplied in a single-dose vial (300mg/30mL) for intravenous infusion.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Xuhong Li	OPQ/OBP/DBRR-IV
Drug Product	Massod Rahimi	OPQ/OBP/DBRR-IV
Immunogenicity	Xuhong Li	OPQ/OBP/DBRR-IV
Labeling	Scott Dallas	OPQ/OBP
Facility	Steve Fong	OPQ/OPF/DIA/BI
Microbiology -DS	Bo Chi	OPQ/OPF/DMA/BIV
Microbiology - DP	Aimee Cunningham	OPQ/OPF/DMA/BIV
Microbiology - QAL	Reyes Candau-Chacon	OPQ/OPF/DMA/BIV
Application Team Lead	Joslyn Brunelle	OPQ/OBP/DBRR-IV
RBPM	Teshara Bouie	OPQ/OPRO

Multi-disciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Natasha Kormanik	OND/OHOP/DHP
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OHOP/DHP
Medical Officer	Rosanna Setse	OND/OHOP/DHP
Pharm/Tox	Ramadevi Gudi	OND/OHOP/DHOT
Clinical Pharmacology	Dipak Pisal	OTS/OCP/DCPII
Statistics	Kate Dwyer	OTS/OB/DBV

Submissions Reviewed:

Submission(s) Reviewed	Document Date
0000	June 18, 2018
Amendment 0007	August 1, 2018
Amendment 0009	August 30, 2018
Amendment 0013	September 26, 2018
Amendment 0014	October 3, 2018
Amendment 0018	October 23, 2018
Amendment 0021	October 26, 2018
Amendment 0024	November 8, 2018
Amendment 0030	November 19, 2018
Amendment 0031	November 20, 2018
Amendment 0032	November 30, 2018
Amendment 0034	December 6, 2018
Amendment 0037	December 11, 2018
Amendment 0038	December 12, 2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:
 - A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	V	(b) (4)	(b) (4)	2	2	2/3/2017 and 4/25/2017	
	III			3	3	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows:
2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed).

- B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
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IND	128367	
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3. Consults: none

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761108 for ULTOMIRIS (ravulizumab-cwvz) manufactured by Alexion Pharmaceuticals Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of ULTOMIRIS 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.

C. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: [REDACTED] (b) (4)
- Drug Product: Alexion [REDACTED] (b) (4)
- Fill size and dosage form: 300mg/30mL vial
- Dating period:
 - Drug Product: 24 months: 2-8 °C
 - Drug Substance: [REDACTED] (b) (4)
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
 - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Rationale: exempted according to 21 CFR 601.2a.

C. Benefit/Risk Considerations:

Ravulizumab-cwvz is a humanized IgG2/4 monoclonal antibody which binds to C5 and prevents activation of the complement cascade. Ravulizumab-cwvz has been evaluated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Eculizumab (approved in 2007) is currently available for treatment of PNH via the same mechanism of action (binding to C5). Ravulizumab-cwvz has the same sequence as Eculizumab, except for 4 point mutations which extend the half-life. The enhanced PK/PD profile, with fewer troughs than Eculizumab, has

potential to improve therapeutic efficacy and reduce treatment burden for patients with PNH while maintaining a safety profile similar to eculizumab. Ravulizumab-cwvz allows maintenance dosing once every 8 weeks compared to Eculizumab (once every 2 weeks). This is 6 infusions per year with ravulizumab compared to 26 infusions per year with eculizumab. This offers improved quality of life through fewer missed days of work or school, better treatment adherence, and improved accessibility.

Alexion’s manufacturing process parameters, in-process controls, release specifications, and stability testing are adequate to ensure product quality for ravulizumab-cwvz. The drug substance and drug product manufacturing processes are well controlled and can reproducibly produce pure and potent product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The drug product manufacturing process provides sterility assurance. The analytical methods for release and stability testing are validated for specificity, precision, repeatability, linearity, accuracy, and robustness. The manufacturing facilities are recommended for approval.

Overall product quality, immunogenicity assay, and labeling (reviewed by OBP), microbiology (reviewed by DMA), facilities (reviewed by DIA) are located as separate documents in Panorama.

D. Postmarketing commitments:

- i. 3557-2: Implement a two-tier Reference material system with (b) (4) storage condition for primary reference material.

Alexion committed by December 31, 2019

- ii. 3557-3: Explore alternative assay formats for the Hemolytic assay in order to reduce the method variability.

Alexion committed by March 31, 2019

- iii. 3557:4: Qualify the (b) (4) sample for the bioburden method using samples from three (b) (4) lots. Provide the qualification data.

Alexion committed by July 31, 2019

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (b) (4)
Fragment (Low Molecular Weight Species (LMWS))	Efficacy, PK, immunogenicity	Manufacturing Process and Storage	(b) (4)

<i>(product-related impurities)</i>			(b) (4)
Aggregates (High Molecular Weight Species (HMWS)) <i>(product-related impurities)</i>	Efficacy, Immunogenicity	Manufacturing Process and Storage	
Disulfide Isoforms – IgG2	Efficacy	Manufacturing Process	
Charge Variants <i>(product-related impurities)</i>	Efficacy	Manufacturing Process and Storage	
Product Peptides <i>(identity)</i>	Identity	Intrinsic to Molecule	
C5 Binding <i>(potency)</i>	Efficacy	Intrinsic to Molecule	
Cell Based Potency <i>(potency)</i>	Efficacy	Intrinsic to Molecule	
Glycosylation <i>(product-related impurities)</i>	PK	Manufacturing process	

B. Drug Substance [ravulizumab-cwvz] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Bioburden <i>(contaminant)</i>	Safety, purity, and efficacy (degradation or modification of product by contaminating microbes)	Raw materials and manufacturing process	(b) (4)
Endotoxin <i>(contaminant)</i>	Safety and purity	Raw materials and manufacturing process	
Appearance <i>(general)</i>	Safety	Manufacturing process and Formulation	
pH <i>(general)</i>	Stability, efficacy	Formulation	
Osmolality <i>(general)</i>	Stability, safety	Formulation	
Protein concentration <i>(general)</i>	Efficacy	Manufacturing process/formulation	
Polysorbate 80 <i>(general)</i>	Stability, efficacy	Formulation	
HCP <i>(process related impurity)</i>	Safety and immunogenicity	Manufacturing process	
DNA <i>(process related impurity)</i>	Safety	Manufacturing process	
(b) (4) <i>(process related impurity)</i>	Safety	(b) (4)	
Mycoplasma and Adventitious agents <i>(process related impurity)</i>	Safety	Contaminaton during manufacture	

- **Description:** Ravulizumab-cwvz is a humanized IgG2/4 monoclonal antibody. The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence. Residues 6 to 36 in the CH2 region are common to both human IgG2 and IgG4 amino acid sequence. The remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions. The molecular weight is (b) (4) Da.

Ravulizumab-cwvz was constructed by introducing four mutations into the heavy chain of eculizumab. Tyr-27-His and Ser-57-His were introduced to the heavy chain variable region (CDR) to destabilize binding to C5 at pH 6.0 with minimal impact on binding to C5 at pH 7.4. Met-429-Leu and Asn-435-Ser were introduced to the third heavy chain constant region domain (CH3) to enhance binding to the human neonatal receptor (FcRn) at pH 6.0 while allowing for efficient release from FcRn at pH 7.4. These mutations significantly increase dissociation of ravulizumab:C5 complexes to free ravulizumab-cwvz in the acidified environment of the early endosome after pinocytosis and to increase the fraction of free ravulizumab-cwvz recycled from the early endosome back into the vascular compartment by FcRn.

Ravulizumab-cwvz has an increased antibody half-life which allows maintenance dosing once every 8 weeks compared to Eculizumab (once every 2 weeks). This is 6 infusions per year with ravulizumab compared to 26 infusions per year with eculizumab. Ravulizumab offers improved quality of life through fewer missed days of work or school, better treatment adherence, and improved accessibility.

- **Mechanism of Action (MoA):** Ravulizumab-cwvz binds to complement protein 5 (C5) and blocks its activation by complement pathway convertases, thus inhibiting the formation of the terminal complement complex. Specifically, inhibits cleavage of C5 into C5a and C5b. C5b is the initiating subunit of the terminal complement complex (C5b-9). By binding specifically to C5, ravulizumab-cwvz antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early components of complement pathway activation that are essential for opsonization of microorganisms and clearance of immune complexes.
- **Potency Assay:** The two potency assays are C5 binding and cell based hemolytic assay.

The C5 binding assay is an ELISA with colorimetric detection. The assay is performed by generating a dose response curve. The activity of the sample is reported relevant to the activity of the reference standard.

The hemolytic assay measures the inhibition of hemolysis of rabbit red blood cells (rRBC) using various concentrations of ravulizumab-cwvz. Normal human serum is added to rRBC in the presence of MgCl₂ and EGTA to activate the complement system. Dose response curves are generated and the relative potency of the sample is determined by comparison to the reference standard. There is a postmarketing

commitment (PMC) to explore alternative assay formats for the hemolytics assay in order to reduce the method variability.

- **Reference Materials:**

[Redacted] (b) (4)

The sponsor has a post marketing commitment (PMC) to implement a two-tier reference material system with [Redacted] (b) (4) storage condition for primary reference material. [Redacted] (b) (4)

- **Critical starting materials or intermediates:**

[Redacted] (b) (4)

- **Manufacturing process summary:**

[Redacted] (b) (4)

There is a PMC to qualify the [Redacted] (b) (4) sample for the bioburden method using samples from three lots manufactured at [Redacted] (b) (4)

- **Container closure:** [REDACTED] (b) (4)
- **Dating period and storage conditions:** [REDACTED] (b) (4)

C. Drug Product ULTOMIRIS Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy (b) (4)
Sterility (<i>contaminant</i>)	Safety (infection), purity and efficacy via degradation or modification of products by contaminating microorganisms	Manufacturing process or container closure integrity failure	[REDACTED]
Endotoxin (<i>contaminant</i>)	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Manufacturing process or container closure integrity failure	
CCIT (<i>sterility assurance</i>)	Safety	Storage conditions	
Protein Content (Concentration) (<i>general</i>)	Efficacy	Formulation	
Osmolality (<i>general</i>)	Safety	Formulation	

pH <i>(general)</i>	Safety	Formulation	(b) (4)
Appearance <i>(general)</i>	Safety	Formulation	
Subvisible Particles <i>(product and/or process-related impurities)</i>	Safety, Immunogenicity	Manufacturing Process and Container Closure System	
Extractable Volume <i>(general)</i>	Efficacy/Dosing	Manufacturing Process	
Extractables/Leachables <i>(process related impurities)</i>	Safety	Manufacturing equipment and Container closure	

- **Potency and Strength:**
Ultomiris is supplied as 10 mg/mL sterile aqueous solution in a stoppered 30 mL glass vial. The extractable volume in the vial is (b) (4)
- **Summary of Product Design:**
Ultomiris is a sterile, single-use, preservative free solution for intravenous infusion that is administered by a healthcare professional. Ultomiris is a liquid, clear to translucent, slight whitish color, and practically free from particles.
- **List of Excipients:**
(b) (4) sodium phosphate, (b) (4) sodium chloride, 0.02% (w/v) Polysorbate 80, pH 7.0
- **Reference Materials:**
The same reference material is used for the Drug Substance and Drug Product.
- **Manufacturing process summary:**
(b) (4)
- **Container closure:**
The primary container closure system for Ultomiris is a 30 mL USP (b) (4) glass vial, a 20 mm (b) (4) rubber stopper (b) (4)

(b) (4) and an aluminum seal with a (b) (4) flip-off cap. The secondary packaging component is a paperboard carton and provides protection from light.

The Sponsor is conducted a leachable study up to 30 months. No leachables have been detected up to 12 months of the study.

- **Dating period and storage conditions:**
24 months at 2 – 8°C

The data included in the BLA support storage for up to 6 hours at ambient temperature and 24 hours at 2 – 8°C when mixed with 0.9% sodium chloride for administration, as described in the labeling.

Post-approval stability protocol allows for extension of shelf-life up to 30months.

- List of co-package components, if applicable: none

D. Any Special Product Quality Labeling Recommendations:

Store at 2 – 8°C. Protect from light. Do not freeze or shake. If not used immediately after dilution in 0.9% sodium chloride, storage times at 2°C – 8°C (36°F – 46°F) must not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted Ravulizumab infusion solution within 6 hours.

E. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
		(b) (4)	PLI conducted (b) (4)	(b) (4)	VAI/Approve
			PLI conducted (b) (4)		VAI/Approve
			In compliance for testing (CTL profile)	N/A	Approve
			In compliance	N/A	Approve

(b) (4)					
				N/A	Approve
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)	Alexion Pharma International Operations Unlimited	3011532960	In compliance for (b) (4) DP manufacture (SVS profile)	N/A	PLI waived; line 1 approved based on 2017 inspection for (b) (4)
	(b) (4)	(b) (4)	In compliance	N/A	Approve
	(b) (4)	(b) (4)	In compliance	N/A	Approve
	(b) (4)	(b) (4)	In compliance for testing (CTL profile)	N/A	Approve

F. Facilities:

Pre-licensing inspections (PLIs) of the DS manufacturing sites (b) (4) facilities were conducted on (b) (4)

(b) (4)

(b) (4)

(b) (4) In both cases the firms were determined to have adequately

addressed the issues and voluntary action indicated (VAI)/Approve decisions were rendered for a biologics DS manufacture profile (profile CBI).

An inspection waiver was issued for the DP manufacturing site, Alexion Pharma International Operations Unlimited (FEI 301153296), based on this firm's current approval for multi-product DP manufacture (b) (4) A PLI was conducted August 10-18, 2017, (b) (4)

G. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

- Qualification of new Working Cell Bank protocol
- (b) (4)
- (b) (4)
- (b) (4)
- Post-approval stability protocol

ii. Outstanding review issues/residual risk: none

iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved:

- Post-approval stability protocol

ii. Outstanding review issues/residual risk: none

iii. Future inspection points to consider: none

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/source material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non-Primate Mammalian Cell Substrate/source material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity	X		
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]			
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation		X
23.		Process		X
24.		Analytical Methods		X
25.		Other		X
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)		X	
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin	X	
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other {fill-in}			



Joslyn
Brunelle

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Joel
Welch

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Reyes
Candau-Chacon

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Zihao Peter
Qiu

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	December 20, 2018
Reviewer:	Scott Dallas Labeling Reviewer Office of Biotechnology Products (OBP)
Through:	Massod Rahimi, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761108
Applicant:	Alexion Pharmaceuticals Inc.
Submission Dates:	June 18, July 3, October 25, November 5, November 15, December 6, December 17 and December 19, 2018
Product:	Ultomiris (ravulizumab-cwvz)
Dosage form:	Injection
Strength and Container-Closure:	300 mg/30 mL (10 mg/mL) in a single-dose vial
Indication, dose, route, and frequency of administration:	Indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion.
Background and Summary Description:	The Applicant submitted an application seeking approval of a new biologic product. The development of ravulizumab for the treatment of PNH has been carried out under IND 128,367. Ravulizumab was granted Orphan Drug Designation on 04 Jan 2017 (#15-5130) for the treatment of PNH.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable from a OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). The prescribing information, medication guide, patient labeling, instructions for use, container labels, and carton labeling were reviewed for compliance with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100, 21 CFR 208.20(a)(7), 21 CFR 208.20(a)(7)).

The prescribing information and medication guide submitted on December 19, 2018, and the container label and carton labeling submitted on November 15, 2018 were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information & Medication Guide (submitted on July 3, 2018)
<\\cdsesub1\evsprod\bla761108\0003\m1\us\draft-labeling-text.doc>
- Container Labels (submitted on June 18, 2018)



- Carton Labeling (submitted on June 18, 2018)



Appendix B: Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
<p><u>Proper Name</u> (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i></p> <p>Comment/Recommendation: To applicant: Include the dosage formulation, injection, to appear below the proper name, Ravulizumab. November 15, 2018: The applicant’s revision is acceptable.</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><u>Manufacturer name, address, and license number</u> (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i></p> <p>Comment/Recommendation: November 6, 2018: Please include the name of the manufacturer, Alexion Pharmaceuticals, Inc. If space permits include the address and U.S. license number. Please refer to 21 CFR 610.60 (a) and (c). Also note, if the only manufacturer information on the label is the licensed manufacturer, then “Manufactured by” phrase may be omitted or abbreviated if additional space is needed for important information. November 15, 2018: The applicant’s revision is acceptable.</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><u>Lot number or other lot identification</u> (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><u>Expiration date</u> (21 CFR 610.60, 21 CFR 201.17)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as “final container”) is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

<p>Multiple dose containers (recommended individual dose) 21 CFR 610.60</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p>Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p>Medication Guide 21 CFR 610.60 21 CFR 208.24</p> <p>Comment/Recommendation:</p> <p>Revise the (b) (4) statement to read "ATTENTION: Dispense the enclosed Medication Guide to each patient". If space is needed on the container label then this statement can be removed from the container label per 21 CFR 610.60(a)(7).</p> <p>November 6, 2018: The container label is considered a partial label the applicant indicated there is not enough space for the statement. The medication guide statement was removed. The revision is acceptable.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p>No Package for container 21 CFR 610.60</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p>Partial label 21 CFR 610.60 21 CFR 201.10</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p>No container label 21 CFR 610.60</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p>Ferrule and cap overseal</p> <p>Comment/Recommendation:</p> <p>Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).</p> <p>November 6, 2018: Alexion confirms that the ferrule and cap overseal of the vial have no text. The information can be found in attachment 3 of Module 3.2.P.7.</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p>Visual inspection 21 CFR 610.60</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

Comment/Recommendation:

Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

November 6, 2018: Alexion responded: At the moment we don't have yet the vial ready but it will look the same as the Soliris' one. The circumference of the vial will be 114.7mm and the length of the label will 108 mm, this leaves a gap of 6.7mm for visual inspection. Alexion's response is acceptable.

NDC numbers

21 CFR 201.2
21 CFR 207.35

- Yes
- No
- N/A

Comment/Recommendation:

If space permits, please include the National Drug Code.

The container label submitted November 15, 2018 contains the NDC.

Route of administration

21 CFR 201.5
21 CFR 201.100

- Yes
- No
- N/A

Comment/Recommendation:

To applicant: Revise [redacted] (b) (4) to read "For Intravenous Use". Delete the reference to [redacted] (b) (4)

November 6, 2018: Alexion responded: The route of administration has been added on the principal display panel directly below the strength presentation. [redacted] (b) (4) has also been deleted.

The November 15, 2018 label displays the statement "for intravenous infusion" which is acceptable.

Preparation instructions

21 CFR 201.5

- Yes
- No
- N/A

Comment/Recommendation:

Package type term

21 CFR 201.5

- Yes
- No
- N/A

Comment/Recommendation:

Revise the package type terminology from (b) (4) to read "Single-Dose Vial" to be consistent with the correct package type terminology presented in the draft prescribing information.

November 6, 2018: Alexion responded: The carton labelling and container labels have been updated to replace (b) (4) by "Single-dose vial-Discard Unused Portion". However, the label contains 2 Single-dose vial-Discard Unused Portion", and one should be deleted.

November 15, 2018: The applicant revised the statement to read "Single-dose vial Discard Unused Portion", and removed one of the statements from the label. The applicant's revisions are acceptable.

Drugs

Misleading statements

21 CFR 201.6

- Yes
- No
- N/A

Comment/Recommendation:

Requesting the terminology "Concentrated Solution" is deleted.

The reference to "Concentrated Solution" has been deleted. The revision is acceptable.

Strength

21 CFR 201.10

21CFR 201.100

- Yes
- No
- N/A

Comment/Recommendation:

To applicant: Revise the abbreviation for milliliter to appear as "mL" with a capital letter "L".

November 6, 2018: Alexion responded and the revised presentation of "mL", which is acceptable.

Drugs

Prominence of required label statements

21 CFR 201.15

- Yes
- No
- N/A

Comment/Recommendation:

To applicant: Revise the statement "CONTAINS NO PRESERVATIVES" to appear as "Contains No Preservatives" capitalizing only the first letter in each word. In addition, consider debolding the statement.

November 6, 2018: Alexion responded and the revised "contains no preservative" statement is acceptable. The revision is acceptable.

Spanish-language (Drugs)

21 CFR 201.16

- Yes
- No
- N/A

<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67 Comment/Recommendation:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Net quantity</u> 21 CFR 201.51 Comment/Recommendation: The presentation of the net quantity is acceptable.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Inactive ingredients</u> 21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Storage requirements</u>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

Comment/Recommendation:

Consider revising the statement (b) (4) to appear as "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the carton."

November 6, 2018: Alexion response -The statement has been revised and is now appearing on the container label as follow: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the carton." Alexion's response is acceptable, but it takes up 2 lines of text.

For space considerations, revise the storage statement to occupy only one line of text. Consider revising the statement to read "Refrigerate at 2°C - 8°C (36°F - 46°F) in carton".

November 15, 2018: The applicant revised the storage statement to read "Refrigerate at 2°C - 8°C (36°F - 46°F) in carton", which appears on one line and is acceptable.

Dispensing container

21 CFR 201.100

- Yes
 No
 N/A

Package (Carton) Label⁵ Evaluation

<u>Regulations, Guidance and CDER Best Labeling Practices</u>	<u>Acceptable</u>
<u>Proper name</u> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10) Comment/Recommendation: To applicant: Confirm the proper name is at least half as large as the proprietary name and the proper name has a prominence commensurate with the prominence with the proprietary name, taking in account all pertinent factors, including typography, layout, contrast, color and other printing features per 21 CFR 201.10 (g)(2). Note historical practices places the dosage form, injection, below the proper name. Refer to <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 326-350)</i> November 6, 2018: Alexion responded: The font size of the proper name has been increased to ensure that it's half of the size of the proprietary name and the font color has been change from grey to black to ensure that it's more readable. The revisions are acceptable.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Manufacturer name, address, and license number</u> 21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Lot number or other lot identification</u>	<input checked="" type="checkbox"/> Yes

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Preservative</u> 21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Number of containers</u> 21 CFR 610.61	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100 To Applicant: Consider increasing the font size of the 10 mg/mL statement to at least half of the prominence of the 300 mg/30 mL statement. November 15, 2018: The applicant increased the font size of the 10 mg/mL statement. The revision is acceptable.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Storage temperature/requirements</u> 21 CFR 610.61 Comment/Recommendation: To Applicant: Revise the statements (b) (4) to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light." To Applicant: Please delete the phrase (b) (4) from the storage statement to be consistent with the prescribing information and eliminate any misinterpretation of the phrase. November 15, 2018: The applicant revised the storage statement to read: Store refrigerated at 2°C – 8°C (36°F – 46°F) in the original carton to protect from light. The applicant also deleted the phrase (b) (4) . The revisions are acceptable.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Handling: "Do Not Shake", "Do not Freeze" or equivalent</u> (21 CFR 610.61)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61	<input type="checkbox"/> Yes <input type="checkbox"/> No

	<input checked="" type="checkbox"/> N/A
<p><u>Route of administration</u> 21CFR 610.61 21 CFR 201.5 21 CFR 201.100</p> <p>Comment/Recommendation: To Applicant: Suggest relocating the route of administration, (b) (4) to appear prominently directly under the strength statement.</p> <p>To Applicant: Remove the phrase (b) (4) from the labeling. Consider revising the statement (b) (4) to read "Dilute with 0.9% Sodium Chloride Injection prior to use." Capitalize the diluent Sodium Chloride Injection.</p> <p>November 6, 2018: Alexion responded: The phrase (b) (4) was deleted and the diluent was presented in capital letters which is acceptable. The applicant also relocated the route of administration statement to appear below the expression of strength. This revision is acceptable.</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Known sensitizing substances</u> 21CFR 610.61</p> <p>Comment/Recommendation: Dr. Rahimi confirmed there are no sensitizing substances.</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Inactive ingredients</u> 21 CFR 610.61 21 CFR 201.100</p> <p>Comment/Recommendation: To Applicant: Revise the inactive ingredients to be in alphabetical order per USP <1091> Labeling of Inactive Ingredients. Polysorbate 80 should appear before the inactive ingredient sodium chloride.</p> <p>November 6, 2018: Alexion responded and revised the inactive ingredients to be listed in alphabetic order, which is acceptable.</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Source of the product</u> 21 CFR 610.61</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Minimum potency of product</u> 21 CFR 610.61</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Rx only</u> 21CFR 610.61 21 CFR 201.100</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<u>Divided manufacturing</u> 21 CFR 610.63	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Distributor</u> 21 CFR 610.64	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<u>Preparation instructions</u> 21 CFR 201.5	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Package type term</u> 21 CFR 201.5	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p>Comment/Recommendation:</p> <p>To Applicant: Revise the package type terminology from (b) (4) to read "Single-Dose Vial" to be consistent with the correct package type terminology in the draft prescribing information.</p> <p>November 6, 2018: Alexion revised (b) (4) to single-dose and relocated a "Single-dose vial-Discard Unused Portion" statement to the principal display panel of the carton.</p> <p>To Applicant: Please delete the hyphen between the words vial and Discard.</p> <p>November 15, 2018: The applicant deleted the hyphen between the phrases "Single-dose vial" and "Discard Unused Portion". The revision is acceptable.</p>	
<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<p><u>Spanish-language (Drugs)</u> 21 CFR 201.16</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Sulfites; required warning statements</u> 21 CFR 201.22</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Net quantity</u> 21 CFR 201.51</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Dispensing container</u> 21 CFR 201.100</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24</p> <p>Comment/Recommendation: To Applicant: Revise the (b) (4) statement to read "ATTENTION: Dispense the enclosed Medication Guide to each patient".</p> <p>November 6, 2018: Alexion responded the Medication Guide statement has been revised to read "Attention: Dispense the enclosed Medication Guide to each patient." and relocated as requested by FDA. The revision is acceptable.</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><u>Other</u></p> <p>Comment/Recommendation:</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: Revise to proprietary name to appear in all capital lettering per the Draft Guidance titled Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM592850.pdf The applicant's response dated Oct 25, 2018 is acceptable.	
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3)	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Comment/Recommendation: September 18, 2018 Dr. Rahimi confirmed that 0.9% sodium chloride injection is the acceptable IV solution. Also confirmed that gently mixing is acceptable, because the applicant performed compatibility studies with 150 rpm shaking. A vigorous shaking study was not conducted. Thus, the "Do not shake" statement proposed by the applicant is appropriate. Also that in-use stability data supports storage for 24 hours at 2- 8°C and 6 hours at room temperature. Therefore, the admixture should be used within 24 hours when stored at 2-8°C to include a maximum time of 6 hours at room temperature. October 1, 2018 Dr. Aimee Cunningham indicated that there are studies in P.2.6 to support 24 hrs at 2-8C and 6 hrs at ambient temperature with a 2-fold safety factor. Dr. Reyes agreed that storage of no more than 6 hrs at room temperature should be added to the label. Proposed wording was added to the label "Once removed from refrigeration, administer the diluted ULTOMIRIS infusion solution within 6 hours."	

October 26, 2018 Dr. Rahimi confirmed the diluted solution should be protected from light and not frozen. These statements were added to the PI labeling. Dr. Rahimi previously confirmed the do not shake statement was appropriate based upon the data or lack thereof submitted.

The PI includes the statement: "Parenteral drug products (b) (4) be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"

October 30, 2018, Dr. Cunningham confirmed micro was ok with the language: If the diluted Ultomiris infusion solution is not used immediately, storage under refrigeration at 2°C – 8°C (36°F – 46°F) must not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted Ultomiris infusion solution within 6 hours.

November 21, 2018, Dr. Rahimi confirmed the applicant provided a justification for the overfill and the overfill volume is acceptable.

3 DOSAGE FORMS AND STRENGTHS

21 CFR 201.57(c)(4)

- Yes
- No
- N/A

Comment/Recommendation:

September 18 & 20, 2018: Dr. Rahimi confirmed the identifying characteristics of "Clear to translucent, slight whitish color".

6.2 IMMUNOGENICITY

Draft Guidance for Industry: Labeling for Biosimilar Products

- Yes
- No
- N/A

Comment/Recommendation:

Updated to reflect the draft Guidance for Industry: Labeling for Biosimilar Products); dated July 2018

The applicant's revised labeling submitted October is acceptable.

11 DESCRIPTION

(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

- Yes
- No
- N/A

Comment/Recommendation:

OBP Labeling: To Applicant: to include the established pharmacological class and cell line per 21 CFR 201.57(c)(12) and 610.61

OBP Labeling- To Applicant: Revised to list all inactive ingredients in alphabetical order (see USP Chapter <1091>) followed by their quantitative information that is deliverable in xx mL using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added (b) (4) or water for injection

OBP labeling: To Applicant: Revised to include the route of administration per 21 CFR 201.57(c)(12)

September 18, 2018 Dr. Rahimi confirmed the product is produced in a CHO cell line, (b) (4) the quantitative information per mL, (b) (4) and the excess volume per vial are acceptable.

The applicant's response dated October 25, 2018 is acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING

21 CFR 201.57(c)(17)

- Yes
- No
- N/A

Comment/Recommendation:

To Applicant: Revised to include the identifying characteristics per 21 CFR 201.57(c)(17)

On September 18, 2018 Dr. Rahimi confirmed the following conditions/information is accurate: Sterile, Preservative-free, Do not Freeze, Do not Shake, Protect from Light, Refrigerate 2°C – 8°C (36°F – 46°F), (b) (4)

The applicant's response dated October 25, 2018 is acceptable.

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64
For NDAs: 21 CFR 201.1

- Yes
- No
- N/A

MEDICATION GUIDE

TITLE (NAMES AND DOSAGE FORM)

- Yes
- No
- N/A

STORAGE AND HANDLING

- Yes
- No
- N/A

INGREDIENTS

- Yes
- No
- N/A

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64
For NDAs: 21 CFR 201.1

- Yes
- No
- N/A

Comment/Recommendation:

To applicant revise the abbreviation for United States to read "U.S."

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on December 19, 2018)
<\\cdsesub1\evsprod\bla761108\0044\m1\us\ultomiris-pi.docx>
- Medication Guide (submitted on December 19, 2018)
<\\cdsesub1\evsprod\bla761108\0044\m1\us\ultomiris-medguide.docx>
- Container Labels (submitted on November 15, 2018)



- Carton Labeling (submitted on November 15, 2018)





Scott
Dallas

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Massod
Rahimi

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 12/4/2018
To: Administrative File, **STN 761108/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead,
CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Applications (BLA)
Applicant: Alexion Pharmaceuticals Inc.
US License: 1743
Facility: [Redacted] (b) (4)

Product: Ultomiris (ravulizumab-cwvz)
Dosage: 300 mg (10 mg/mL), Sterile parenteral solution for intravenous infusion
Indications: Treatment of adult patients with paroxysmal nocturnal hemoglobinuria
PDUFA date: February 18, 2019

Recommendation: The drug substance part of this BLA is recommended for approval from quality microbiology perspective with the following post-marketing commitment:

Qualify the [Redacted] (b) (4) sample for the bioburden method using samples from three [Redacted] (b) (4) lots. Provide the qualification data.

Review Summary

Alexion has submitted this Biologics License Application (BLA) for ravulizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria. The drug substance (DS) is manufactured at [Redacted] (b) (4). The drug product (DP) is manufactured at Alexion [Redacted] (b) (4). The application contains CMC information in an eCTD format.

This review contains an assessment of the ravulizumab drug substance section of the BLA from microbiology perspective. The amendments reviewed are provided in the table below:

Sequence number	Date	Description
0001	6/18/2018	Original BLA submission
0013	9/26/2018	Response to IR

0024	11/8/2018	Response to IR
0032	11/30/2018	Response to IR

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Ravulizumab is a recombinant humanized IgG2/4 monoclonal antibody that binds to the human complement component 5 (C5) and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b. Ravulizumab was constructed by introducing four unique mutations into the heavy chain of eculizumab. Ravulizumab is expressed using Chinese hamster ovary (CHO) cells. The DS and DP formulation contains ravulizumab at a concentration of 10 mg/mL in (b) (4) sodium phosphate, (b) (4) sodium chloride, 0.02% (w/v) Polysorbate 80.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Drug substance manufacturing, Drug substance in-process and lot release (endotoxin and bioburden)

(b) (4)

Drug substance manufacturing, Drug substance in-process, lot release, and stability testing

(b) (4)

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)

(b) (4)



Bo
Chi

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Reyes
Candau-Chacon

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Acting Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA: 761108/0
Applicant: Alexion Pharmaceuticals, Inc.
US License Number: 1743
Submission Reviewed: Original BLA
Product: Ultomiris (ravulizumab-cwvz)
Indication: adults with paroxysmal nocturnal hemoglobinuria
Dosage Form: solution for i.v. infusion
Manufacturing Sites: Alexion [REDACTED] (b) (4)
[REDACTED]
FDA Receipt Date: 06/18/2018
Action Date: 02/18/2019

Conclusion and Approvability Recommendation

The drug product section of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	06/18/2018	Original BLA submission
0007	08/01/2018	IR responses
0009	08/30/2018	Update to BLA
0013	09/26/2018	IR responses
0018	10/23/2018	IR responses

Letters of authorization for the following DMFs for the stoppers were provided in amendment 0013; the review status of the DMFs related to this BLA is documented below.

DMF #	Content	Date Reviewed	Finding	Document Name
	(b) (4)	02/03/2017	Adequate	(b) (4).doc
		04/25/2017	Adequate	(b) (4).doc

Module 1

1.14 Labeling

Ravulizumab is administered using weight-based dosing. There is a loading dose and maintenance dose, both given by i.v. infusion. Vials are single-use and must be diluted to 5 mg/mL in 0.9% NaCl prior to infusion. Prepared solution should be administered immediately and must be processed through a 0.22 µm filter. If DP is not used immediately, the storage time at 2-8°C cannot exceed 24 hrs including the expected infusion time. Admixtures should be allowed to adjust to room temperature prior to infusion and cannot be heated in a microwave or any other heat source than ambient air temperature.

Reviewer's Note: An admixture microbial challenge study to support the label is provided in P.2.6. The label was updated to include that the admixture cannot remain at room temperature for longer than 6 hrs.

SATISFACTORY

Module 3.2

P.1 Description and Composition of the Drug Product

DP is a sterile solution for i.v. infusion containing 10 mg/mL ravulizumab in (b) (4) sodium phosphate (b) (4) (b) (4) sodium chloride (b) (4) 0.02% (w/v) polysorbate 80 (b) (4). All excipients are compendial, and DP is diluted in commercially available 0.9% saline for infusion. The drug product composition is defined in table 1 of this section of the BLA. The container closure system is a 30 mL (b) (4) glass vial, with a (b) (4) rubber stopper (b) (4), and an aluminum seal with a (b) (4) flip-off cap.

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)



Aimee
Cunningham

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Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
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