CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761107Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING REVIEW

Date of review:	November 14, 2018
Reviewer:	Scott Dallas, RPh, Labeling Reviewer Office of Biotechnology Products (OBP)
Through:	Riley Myers, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761107
Applicant:	Novimmune S.A.
Labeling Submission Dates:	March 20; August 23; September 4, 14 and 19; October 5, 12, 24, 25, 30 and 31; November 9, 2018
Product:	Gamifant (emapalumab-lzsg)
Dosage form:	Injection
Strengths and Container-Closure:	10 mg/2 mL (5 mg/mL) and 50 mg/10 mL (5 mg/mL) single-dose vial
Indication, dose, route, and frequency of administration:	(b) (4) The recommended starting dose of GAMIFANT is 1 mg/kg given as an intravenous infusion over 1 hour. GAMIFANT should be administered twice a week (every 3 to 4 days) until hematopoietic stem cell transplantation (HSCT) is performed. The GAMIFANT dose may be increased to 3 mg/kg then to 6 mg/kg and up to 10 mg/kg depending on clinical and laboratory parameters including fever, platelet counts, Absolute Neutrophil Count (ANC), ferritin, splenomegaly, and coagulopathy (D-Dimer or Fibrinogen).
Background and Summary Description:	The Applicant submitted an original Biologics License Application for the treatment of patients with primary hemophagocytic lymphohistiocytosis (HLH). Orphan drug designation was granted for the treatment of HLH (Orphan Product Designation #10-3029; Date Designated March 26, 2010) and rare pediatric disease designation was granted for the treatment of primary HLH (Rare Pediatric Disease Designation# RPD-2017-129; Date Designated August 25, 2017). Breakthrough therapy designation was granted for the treatment of HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy on March 11, 2016.
Recommendations:	The prescribing information, medication guide, container labels and carton labeling are acceptable from a quality 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 to the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) nomenclature and labeling standards, and CDER labeling practices and guidances.

The prescribing information, medication guide, container labels, and carton labeling were reviewed and found to be acceptable 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), USP standards, and CDER labeling practices and guidances.

The labels and labeling submitted on October 31 and November 9, 2018 are acceptable (see Appendix C) from a OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on March 20, 2018)
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- Container Labels (submitted on March 20, 2018)
  10 mg/2 mL vial label

(b) (4)

50 mg/10 mL vial label

- Carton Labeling (submitted on March 20, 2018)

  10 mg/2 mL carton labeling

50 mg/10 mL carton labeling

Appendix B: Evaluation Tables
Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation
10 mg/2 mL and 50 mg/10 mL

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** Ensure nonproprietary name is at least half as large as the proprietary name and shall have a commensurate prominence per 21 CFR 201.10(g)(2). Please provide font sizes of the proprietary and proper names. Novimmune SA response dated September 4, 2018: The Sponsor confirms that the nonproprietary name is at least half as large as the proprietary name on the container and carton labels.	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* **Comment/Recommendation:** Revise the (b) (4) to read "Manufactured by:" or "Mfd. by:" Also if the only manufacturer information on the label is the licensed manufacturer, then "Manufactured by" phrase as well as the address may be omitted if additional space is needed for important information per 21 CFR 610.60(c). Novimmune SA revision is acceptable.	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) **Comment/Recommendation:** There is a placeholder for the lot and expiration date.	☐ No ☒ Yes ☐ N/A

[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.

Expiration date (21 CFR 610.60, 21 CFR 201.17) **Comment/Recommendation:** There is a placeholder for the lot and expiration date with a format of MM-YYYY.	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60 **Comment/Recommendation:**	☐ No ☐ Yes ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100 **Comment/Recommendation:** Consider debolding the "Rx Only" to allow for prominence of other critical information on the label. Novimmune SA response revision is acceptable.	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 **Comment/Recommendation:**	☐ No ☐ Yes ☒ N/A
No Package for container 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10 **Comment/Recommendation:**	☐ No ☒ Yes ☐ N/A
No container label 21 CFR 610.60 **Comment/Recommendation:**	☐ No ☐ Yes ☒ N/A
Ferrule and cap overseal	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
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).

Novimmune SA response dated September 4, 2018:
The Sponsor confirms that there is no text on the cap overseal. The only information on the vial ferrule skirt is the lot number, which is in compliance with USP Chapter <7>.

Visual inspection 21 CFR 610.60	☐ No ☒ Yes ☐ 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).

Novimmune SA response dated September 4, 2018:
Novimmune confirmed there is space for visual inspection of the contents.

NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
Please provide your National Drug Codes for review.

Novimmune SA response dated October 24, 2018: The NDC are acceptable.

Novimmune SA revised the NDC with the labeling submitted on November 9, 2018. The NDC number is acceptable.

Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Revise the package type term from [redacted] (b) (4) to "Single-dose vial". The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to *Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015*

Novimmune SA response dated September 4, 2018:
The package term was revised to read "single-dose".

Drugs **Misleading statements** 21 CFR 201.6	☐ No ☐ Yes ☒ N/A
Strength 21 CFR 201.10 21CFR 201.100	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Ensure the linear bar code appears on the label. We recommend providing a copy of the label with a bar code. *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* and *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*

Novimmune SA response dated October 24, 2018:
As discussed on the October 16, 2018 teleconference with FDA, the Sponsor agrees to add a linear NDC barcode to the GAMIFANT (emapalumab-lszg) container labels. The Sponsor has increased the size of the vial label for the 10 mg dosage strength of GAMIFANT from 16 mm to 21 mm to accommodate this request. Provided in this submission is revised container (vial) artwork for the GAMIFANT 10 mg and 50 mg strengths that includes the linear barcode.

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Storage requirements	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:
The label includes refrigerate and protect from light statements but does not include Do not freeze or shake statements due to lack of space.

Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label[5] Evaluation
10 mg/2 mL and 50 mg/10 mL

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10) **Comment/Recommendation:** Ensure nonproprietary name is at least half as large as the proprietary name and shall have a commensurate prominence per 21 CFR 201.10(g)(2). Please provide font sizes of the proprietary and proper names. Novimmune SA response dated September 4, 2018: The Sponsor confirms that the nonproprietary name is at least half as large as the proprietary name on the container and carton labels.	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61 **Comment/Recommendation:** Revise the (b) (4) to read "Manufactured by" when referring to Novimmune SA. Revise the (b) (4) to read "Manufactured at" when referring to Patheon Italia SpA. To comply with 21 CFR 610.61(b), the manufacturer information should appear as the name and address of the manufacturer listed as the applicant on FDA form 356h. Relocate the U.S. license number information to appear directly after the manufacturer name and address. Novimmune SA response dated September 4, 2018: The sponsor's revisions are acceptable.	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Preservative	☐ No

[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 **Comment/Recommendation:** Confirmed no preservative included	☒ Yes ☐ N/A
Number of containers 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Storage temperature/requirements 21 CFR 610.61 **Comment/Recommendation:** Revise the storage statement "Storage: 36ºF to 46ºF (2ºC to 8ºC) . (b) (4) to read "Store refrigerated at 2ºC to 8ºC (36ºF to 46ºF) in original carton to protect from light." DMEPA has a similar statement which is acceptable. Novimmune SA response dated September 4, 2018: The sponsor revision is acceptable and includes Do not freeze or shake.	☐ No ☒ Yes ☐ N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21CFR 610.61 **Comment/Recommendation:**	☒ No ☐ Yes ☐ N/A

There are no known sensitizing substances

Inactive ingredients
21 CFR 610.61
21 CFR 201.100

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Revise the order of the inactive ingredients Sodium chloride and Polysorbate to appear as Polysorbate 80 (0.05 mg) and Sodium chloride (7.3 mg) to ensure the ingredients are listed in alphabetical order.

In the Contents statement: Please correct the spelling of the active ingredient from "empalumab" to "emapalumab".

Novimmune SA response dated September 4, 2018:
The sponsor's revision is acceptable.

Source of the product
21 CFR 610.61

☐ No
☐ Yes
☒ N/A

Comment/Recommendation:

Minimum potency of product
21 CFR 610.61

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:
There is no standard of potency. The carton contains a statement.

Rx only
21CFR 610.61
21 CFR 201.100

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Distributor
21 CFR 610.64

☐ No
☐ Yes
☒ N/A

Comment/Recommendation:

Bar code
21 CFR 610.67
21 CFR 201.25

☐ No
☒ Yes
☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Novimmune SA revised the NDC with the labeling submitted on November 9, 2018. The NDC number is acceptable.	
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Revise the package type statement from (b) (4) to "Single-dose vial". Novimmune SA response dated September 4, 2018: The Sponsor has replaced this statement according to FDA's recommendation on the container and carton labels.	
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55	☐ No ☒ Yes

21 CFR 201.100	☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
Other **Comment/Recommendation:**	☐ No ☐ Yes ☒ N/A

Prescribing Information

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2) Revise the capital letter "I" to a small letter "i".	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Injection: • 10 mg/2 mL (5 mg/mL) solution in a single-dose vial • 50 mg/10 mL (5 mg/mL) solution in a single-dose vial To Applicant: The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to *Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and*	

Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015

To Applicant: Per USP General Chapters: <7> Labeling, for injectable products with containers that supply a volume of drug greater than 1 mL, the primary expression of strength is the strength per total volume followed in close proximity by a parenthetical that includes the strength/mL. We revised the strength presentation to read "10 mg/2 mL (5 mg/mL)" and "50 mg/10 mL (5 mg/mL)"

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION
21 CFR 201.57(c)(3)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Revise [redacted] (b) (4) to read 0.9% Sodium Chloride Injection, USP

The storage of the prepared product reads:
If not administered immediately:
- Store the diluted solution of GAMIFANT under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of dilution. (Section 3.2.P.2.6)
- If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Do not freeze. Do not shake.

The administration section reads to infuse over 1 hour.

August 1, 2018
Dr. Myers confirmed the product should not be shaken. [redacted] (b) (4)

Thus, the "no more than 4 hours" is a standard micro time limit.

The product t should be refrigerated and not frozen thus the "Do not freeze" statement.

Dr. Swisher confirmed a [redacted] (b) (4) statement is not needed for the diluted solution [redacted] (b) (4) (If the diluted solution is not administered immediately, then it can be stored under refrigeration for no more than 4 hours from time of dilution).

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

clear to slightly opalescent, colorless to slightly yellow preservative-free solution

August 1, 2018 Dr. Myers confirmed the identifying characteristics are acceptable.

To Applicant: Per USP General Chapters: <7> Labeling, for injectable products with containers that supply a volume of drug greater than 1 mL, the primary expression of strength is the strength per total volume followed in close proximity by a parenthetical that includes the strength/mL. We revised the strength presentation to read "10 mg/2 mL (5 mg/mL)" and "50 mg/10 mL (5 mg/mL)"

- 10 mg/2 mL (5 mg/mL) solution in a single-dose vial
- 50 mg/10 mL (5 mg/mL) solution in a single-dose vial

6.2 IMMUNOGENICITY
Draft Guidance for Industry: Labeling for Biosimilar Products

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

To applicant: Revised the first paragraph to be consistent with the Draft Guidance: Labeling for Biosimilar Products, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf

"As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies* (b) (4) *in the studies described below with the incidence of antibodies in other studies or to other products may be misleading."*

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))

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

To Applicant: (b) (4)

To Applicant: Revised the second paragraph to include the proper name, dosage formulation and the route of administration per 21 CFR 201.57(c)(12).
Revised the second paragraph to read
GAMIFANT (emapalumab) injection for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution provided in single-dose vials that require dilution prior to intravenous infusion.

Revised the 3rd paragraph to read

Each vial contains 10 mg/2 mL or 50 mg/10 mL emapalumab-lzsg at a concentration of 5 mg/mL. Each mL also contains the following inactive ingredients: L-Histidine (1.55 mg), L-Histidine monohydrocloride, monohydrate (3.14 mg), Polysorbate 80 (0.05 mg), sodium chloride (7.3 mg), and Water for Injection, USP.

August 1, 2018 Dr. Myers confirmed the ingredients and quantities per mL are accurate.

(b) (4)

Dr. Myers confirmed the product is an interferon gamma (IFNγ) blocking antibody.

16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Insertion of the proper name into the first sentence

August 1, 2018 Dr. Myers confirmed that confirm the conditions Protect from light, and Do not shake or freeze are accurate. Also the product does not contain a preservative and there is no U.S. standard of potency.

MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

To comply with 21 CFR 610.61(b), we revised the manufacturer information to appear as the name and address of the manufacturer listed as the applicant on FDA form 356h. We relocated the U.S. license number information to appear after the manufacturer name and address.
The drug manufacturing site (Patheon Italia S.p.A. Ferentino Italy) may be included if the requirements for 21 CFR 610.61(b) are met.

Revised to comply with 21 CFR 610.64 Name and address of distributor.

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
STORAGE AND HANDLING	☐ Yes ☐ No

	☒ N/A
Comment/Recommendation: This product is administered by healthcare providers, so this info is not included.	
INGREDIENTS	✓ Yes ☐ No ☐ N/A
MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on November 9, 2018)
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- Medication Guide (submitted on October 31, 2018)
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- Container Labels (submitted on November 9, 2018) 10 mg/2 mL

- Container Labels (submitted on November 9, 2018) 50 mg/10 mL

- Carton Labeling (submitted on November 9, 2018) 10 mg/2 mL

(b) (4)

- Carton Labeling (submitted on November 9, 2018) 50 mg/10 mL


(b) (4)

Scott Dallas

Digitally signed by Scott Dallas
Date: 11/15/2018 09:22:39AM
GUID: 508da712000294048aa136a18a6af06a

Riley C Myers

Digitally signed by Riley C Myers
Date: 11/15/2018 10:06:53AM
GUID: 57f6809300502f3978f97f5b5a09d128

First Approval for Indication
Breakthrough Review, Priority Review

Recommendation: Approval

BLA 761107
Review

Date: October 25, 2018

From: Jennifer Swisher, Ph.D.
Team Leader, DBRR I/OBP/OPQ

Through: Rachel Novak, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Drug Name/Dosage Form	**Gamifant (emapalumab-lzsg)/injection**
Strength/Potency	**10 mg/2.0 mLand 50 mg/10.0 mL (5 mg/mL concentration)**
Route of Administration	**Intravenous infusion**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy**
Applicant/Sponsor	**NovImmune S.A.**
US agent, if applicable	**Advyzom, LLC**

Product Overview

Emapalumab-lzsg is a human IgG1λ monoclonal antibody produced in CHO cells. Emapalumab targets soluble and receptor-bound forms of interferon gamma (IFNγ) and is a non-competitive inhibitor of the IFNγ receptor (IFNGR) that prevents the signaling of the IFNγ receptor and STAT-1 dependent signaling cascades downstream. Emapalumab drug product is supplied as a sterile, single-dose, preservative-free solution for intravenous infusion in single-dose vials containing 10 mg/2.0 mL or 50 mg/10.0 mL. Emapalumab is proposed for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Riley Myers	DBRR I/OBP/OPQ
Drug Product	Riley Myers	DBRR I/OBP/OPQ
Immunogenicity	Riley Myers	DBRR I/OBP/OPQ
Labeling	Scott Dallas	OBP/OPQ
Facility	Ziyang Su	DIA/OPF/OPQ
Microbiology (DS)	Scott Nichols	DMA/OPF/OPQ
Microbiology (DP)	Candace Gomez-Broughton	DMA/OPF/OPQ
Business Process Manager	Anita Brown	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Jennifer Swisher	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Rachel Novak	DBRR I/OBP/OPQ
Microbiology Team Lead	Maria Reyes Candau-Chacon	DMA/OPF/OPQ
Facilities Team Lead	Zhihao Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Natasha Kormanik	DHP/OHOP/OND
Cross-disciplinary Team Lead	Tanya Wrobleski	DHP/OHOP/OND
Medical Officer	Margaret Merino	DHP/OHOP/OND
Pharm/Tox	Pedro DelValle and Christopher Sheth (TL)	DHOT/OHOP/OND
Clinical Pharmacology	Christy John, Gene Williams (TL) Gopichang Gottipati, Lian Ma (TL)	OTS/OCP/DCPV OTS/OCP/DCPI
Stats	Jingjing Ye, Lei Nie, and Thomas Gwise (TL)	DBII/OB/OTS

a. Names
   i. Proprietary Name: Gamifant
   ii. Trade Name: Gamifant
   iii. Non-Proprietary/USAN: emapalumab
   iv. INN Name: emapalumab
   v. OBP systematic name: MAB HUMAN (IGG1) ANTI P01579 (IFNG_HUMAN) [NI0501]

b. Pharmacologic category: Interferon gamma-directed neutralizing monoclonal antibody

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Team Lead	Maria Reyes Candau-Chacon	See Panorama
Facilities Branch Chief	Peter Qiu	See Panorama
Team Lead OBP/DBRRI	Jennifer Swisher	See Panorama
Review Chief OBP/DBRRI	Rachel Novak	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
STN 761107/1	3/20/2018	OBP
STN 761107/4	5/11/2018	DMA, OBP
STN 761107/6	6/8/2018	DMA
STN 761107/7	6/15/2018	OBP
STN 761107/10	6/25/2018	OBP
STN 761107/12	7/6/2018	OBP
STN 761107/13	7/27/2018	OBP
STN 761107/14	8/1/2018	DMA
STN 761107/16	8/16/2018	DIA
STN 761107/18	8/30/2018	OBP
STN 761107/19	8/31/2018	OBP
STN 761107/20	8/31/2018	OBP
STN 761107/22	9/6/2018	DMA
STN 761107/25	10/4/2018	OBP
STN 761107/28	10/15/2018	DMA
STN 761107/30	10/19/2018	OBP
STN 761107/34	10/29/2018	OBP
STN 761107/36	10/31/2018	DMA

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]
(b) (4)	Type V		(b) (4)	1	Adequate
	Type V			1	Adequate
	Type III			3	N/A
	Type III			3	N/A
	Type III			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 enough data in the application, therefore the DMF did not need to be reviewed)

C. Other Documents: None

3. **CONSULTS:** none

Product Quality Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761107 for Gamifant (emapalumab) manufactured by NovImmune, SA. The data submitted in this application are adequate to support the conclusion that the manufacture of emapalumab 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.

b. Approval action letter language

- Manufacturing location:
  - Drug Substance – (b) (4)
  - Drug Product manufacturing, labeling, and packaging– Patheon Italia S.p.A, 2 Trav. SC Via Morolense, 5, Ferentino, Italy
- Fill size and dosage form – 10 mg/2 mL and 50 mg/10 mL, injection, in single-dose vials
- Dating period:
  - Drug Substance: (b) (4) months; ≤ (b) (4) °C
  - Drug Product: 36 months; 2-8°C
  - Protocols for the extension of DS and DP expiry periods are approved
- Exempt from lot release
  - Yes. Exemption of specified products according to 601.2a

c. Benefit/Risk Considerations

Emapalumab is proposed as a treatment for adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. There are no drugs currently approved for the treatment of HLH, although immuno-chemotherapy (such as the combination of dexamethasone and etoposide) is used to reduce inflammation in HLH patients. This drug demonstrates improvement over existing therapies for this serious and life threatening disease. This also represents the first therapeutic to specifically target the IFNγ pathway. IFNγ is involved in the recruitment and activation of multiple immune cell types and is believed to play a major role in the pathology of HLH. Emapalumab binds to IFNγ and inhibits downstream immune activation.

The overall control strategy for emapalumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of Drug Substance (DS) and Drug Product (DP), and stability of these materials. The currently proposed manufacturing control strategy, in-process controls, process monitoring tests, release, and stability testing is sufficient to ensure

process consistency and that DS and DP are of adequate quality and are free of adventitious agents.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if Approvable

1. To re-evaluate emapalumab drug substance lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications should be provided in the final report.

2. To re-evaluate emapalumab drug product lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

3. To complete the development of an assay to detect host-cell proteins with improved sensitivity, and to re-evaluate host cell protein release acceptance criteria following analysis of all clinical, PPQ, and commercial drug substance lots with the improved host cell protein assay. The corresponding validation report, data, analysis and the statistical plans used to evaluate the specifications, and the proposed change to the specification should be provided in the final report.

4. To complete your investigations into the root-cause, prevalence and size distribution of the visible particles in your clinical, PPQ, and commercial drug substance lots, and based on these investigations, propose a control strategy for visible particles in your final drug substance to ensure successful manufacture of the drug product and ensure that it will be “free from visible particles”.

5. To perform a leachable study to evaluate the filled drug product container closure systems through the end of shelf-life when stored inverted under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance and drug product.

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

Table 1: Drug Substance (DS) and Drug Product (DP) CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
Potency	Efficacy	Intrinsic to the molecule. Impacted by oxidation, fragmentation, and aggregation. Minimal change is expected during storage through expiry.	(b) (4)	Although NI-0501 can bind the IFNγ receptor, no appreciable ADCC or CDC activity was detected.
Identity	Safety and Efficacy	Intrinsic to the molecule		
Oxidation	Efficacy and Safety/Immunogenicity	Manufacturing process and exposure to heat stress		
Glycosylation (aglycosylated species)	PK	(b) (4) No change is expected during storage.		

			(b) (4)	
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Safety/Immunogenicity, Efficacy, and potentially PK	Manufacturing process and exposure to heat stress. Minimal change is expected during storage through expiry.		
Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat and potentially extreme light stress. Minimal change is expected during storage through expiry.		N/A

Glycosylation (b) (4)	PK	(b) (4) No change is expected during storage.	(b) (4)	N/A
Osmolality*	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
pH*	Safety and Efficacy	Formulation		N/A
Protein Content*	Efficacy	Manufacturing process		N/A
Polysorbate 80*	Safety and efficacy (control of degradation)	Formulation		N/A

* Sponsor did not name these attributes as CQAs, however these were tested as part of DS and DP release.

B. Drug Substance [emapalumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	(b) (4)
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A

			(b) (4)	
Residual (b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related (b) (4)		N/A
Residual (b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		N/A

Leachables (Process-related impurity)	Safety	Process-related impurities potentially from manufacture and the DS container closure system	(b) (4)	N/A
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through raw materials and throughout the manufacturing process		N/A

a. Description

Emapalumab is a recombinant, human IgG1λ monoclonal antibody and consists of two heavy chains that are each composed of 453 amino acids and two light chains that are each composed of 217 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 303 (Asn303). The molecular weight of deglycosylated emapalumab is 145,098 Da.

The extinction coefficient was calculated and confirmed experimentally to be (b) (4) $(mg/mL)^{-1} cm^{-1}$. The theoretical value of (b) (4) $(mg/mL)^{-1} cm^{-1}$ has been used during development and will continue to be used to determine the emapalumab protein concentration for commercial use.

b. Mechanism of action

Emapalumab binds to soluble and receptor-bound IFNγ and inhibits receptor signaling via Stat1. Although emapalumab is not a competitive inhibitor of IFNGR binding, its binding reduces IFNγ affinity for its receptor. Despite receptor binding, it has been demonstrated not to elicit effector functions (CDC or ADCC) in vitro and is internalized when bound to the IFNγ/IFNGR complex. IFNγ is expressed predominantly by T cells, NK cells, and macrophages and amplifies innate immune responses through multiple pathways, such as modulation of MHC I and II antigen presentation, enhancing macrophage activation and responsiveness to inflammatory stimuli, and priming or increasing the expression of effector genes, such as those for other cytokines that in turn recruit and/or activate additional immune cell populations. Elevated IFNγ is found in patients with HLH and is thought to underlie much of the pathology of this disease.

c. Potency Assay

A cell-based bioassay that measures the inhibition of STAT1 signaling downstream of the IFNGR is used to control DS and DP potency. Emapalumab samples are pre-incubated with IFNγ before being added to HeLa cells engineered to express the IFNGR and a luciferase reporter gene under control of a STAT1 binding element. The addition of emapalumab leads to the inhibition of IFNGR signaling through the Jak/STAT pathway and, thus, the inhibition of luciferase-based fluorescence driven by the STAT1 promoter element. The amount of luciferase generated is measured using a chemiluminescent substrate and the inhibition is proportional to inhibition of IFNGR signaling. Dose-response curves are analyzed, and the potency of test articles is calculated as a percentage relative to the reference standard (RS).

d. Reference Standard(s)

(b) (4)

e. Critical starting materials or intermediates

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

The DS stored in (b) (4) . The container closure system is suitable for emapalumab, based on stability data.

h. Dating period and storage conditions

The dating period for the DS will be (b) (4) months when stored at ≤ (b) (4) C.

C. Drug Product [emapalumab] Quality Summary

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

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (DP) (contaminant)	Safety (infection) and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination introduced throughout DP manufacturing process or due to failure of container closure integrity	(b) (4)	
Container Closure Integrity (contaminant)	Safety (contamination)	Manufacturing failure or impact of storage conditions		N/A
Endotoxin (contaminant)	Safety and Purity	Contamination introduced throughout DP manufacturing process or due to failure of container closure integrity		N/A
Color and turbidity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A

Particulate Matter (translucent, visible and subvisible) (Product or Process Related Impurities)	Safety/ Immunogenicity	Manufacturing process and CCS	(b) (4)	N/A
Polysorbate 80 quality and concentration	Safety and Efficacy (control over degradation)	Raw material sources, manufacturing process		N/A
Extractable Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		Based on the extractables studies and stability data, as well as 6 month leachable study on the CCS, the risk from leachables is low; however, leachable studies should be performed on the CCS for the duration of the proposed shelf-life to confirm this conclusion. The applicant has committed to a PMC for these studies.

a. Potency and Strength

Emapalumab is supplied at 5 mg/mL in 10 mg/2.0 mL and 50 mg/10.0 mL vials. Potency is defined as the percent activity relative to the current emapalumab RS. The potency assay is the same as described in the DS section of this memo.

b. Summary of Product Design

Emapalumab is supplied as a sterile, single-dose, preservative-free solution in a (b) (4) glass vial for intravenous infusion. Emapalumab DP is formulated in 25 mM histidine / histidine hydrochloride, 125 mM sodium chloride, 0.005% polysorbate 80, pH 6.0. The extractable volumes are 2.0 mL and 10.0 mL.

c. List of Excipients

Excipients include L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, hydrochloric acid, and sodium hydroxide. All excipients are compendial. The histidine hydrochloride monohydrate and sodium hydroxide follow the requirements of Ph.Eur. because there is no USP monograph/chapter for these materials.

d. Reference material(s)

The same reference material is used for DS and DP.

e. Manufacturing process summary

The DP is manufactured at Patheon, Ferentino, Italy. The DP manufacturing process consists (b) (4) . The DP is stored at 2-8°C.

The control strategy is considered adequate to ensure (b) (4) consistently accurate fill and adequate critical quality attributes.

f. Container closure

The primary container closure systems for emapalumab DP consists of 2 and 10 mL (b) (4) glass vials (b) (4) rubber stoppers (b) (4) and aluminum (b) (4) white flip-off caps (b) (4) for 2 and 10 mL vials, respectively).

g. Dating period and storage conditions

The dating period for emapalumab DP will be 36 months when stored at 2-8ºC.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
- Store in original carton (b) (4)
- Protect from light (b) (4)
- Do not freeze.
- Do not shake.

F. Establishment Information

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
Site Name	**Address**	**FEI/DUNS Number**	**Responsibility**	**Final Recommendation**
(b) (4)			Drug Substance manufacture and Storage; Drug Substance release and stability testing	Acceptable based on (b) (4)
			Drug Substance release testing (b) (4)	Approve based on facility profile
			Potency testing for Drug Substance release and stability testing	Approve based on facility profile
			Testing of cell banks for viruses and non-viral adventitious agents, (b) (4) viruses and mycoplasmas	Approve based on facility profile
			Testing of MCB/WCB for viruses	Approve based on facility profile
			Drug Substance storage and shipping	Approve based on facility profile
DRUG PRODUCT				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
Patheon Italia S.p.A	2° Trav. SX Via Morolense, 5 03013-Ferentino (FR) Italy	FEI# 3004110157	Drug Product manufacture (b) (4)	Acceptable based on PAI of 9/10-21/2018

(b) (4)	Drug Product release testing (b) (4)	Approve based on facility profile
	Potency testing for Drug Product release and stability testing	Approve based on facility profile
	Container closure integrity testing for stability studies	Approve based on facility profile
	(b) (4)	Approve based on facility profile
	Labelling, secondary packaging, storage, and distribution of Drug Product	Approve based on facility profile
	Drug Product storage and distribution	Approve based on facility profile

G. Facilities

The BLA proposes commercial manufacture of emapalumab (b) (4) DP at (b) (4) Patheon Italia S.p.A (FEI: 3004110157) (b) (4) DS and DP release and stability testing will also occur at (b) (4)

A pre-licensure inspection (PLI) of the drug substance (b) (4) manufacturing facility was conducted at (b) (4) The initial field recommendation for the firm is VAI and approval of BLA 761107/0. A two-item FDA-483 was issued. An OPF/DIA review of the inspection deemed the firm's 483 response adequate and recommended approval of the facility in regard to BLA 761107. The inspection was classified as VAI. The compliance status of this emapalumab DS manufacturing facility is acceptable.

A joint surveillance and pre-license inspection of the drug product manufacturing facility was conducted at Patheon Italia S.p.A on September 10-21, 2018 by ORA. The initial field recommendation for the firm is VAI and approval of BLA 761107/0. A three-item FDA-483 was issued at the end of the inspection. An OPF/DIA review of the inspection deemed the firm's 483 response adequate and recommended approval of the facility in regard to BLA 761107. The inspection was classified as VAI. The compliance status of this emapalumab DP manufacturing facility is acceptable.

H. Lifecycle Knowledge Management

a. Drug Substance
   i. Protocols approved: (b) (4) annual stability and protocol for extension of expiry
   ii. Outstanding review issues/residual risk: See PMCs 1, 3, and 4
   iii. Future inspection points to consider: Visible particle testing, requalification of reference standards, temperature and environmental control of the manufacturing facility

b. Drug Product
   i. Protocols approved: Annual stability and stability extensions for Drug Product
   ii. Outstanding review issues/residual risk: See PMCs 2 and 5
   iii. Future inspection points to consider: Visual testing, quality of investigations regarding manufacturing and laboratory deviations

Jennifer Swisher

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Rachel Novak

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

To: Administrative File, STN 761107/0
From: Ziyang Su, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 2082
Applicant: Novimmune SA
Mfg. Facility: Drug Substance (b) (4)

Drug Product *Patheon Italia S.p.A,* Ferentino, Italy
FEI 3004110157

Product: Emapalumab, Solution for injection
Dosage: 50 mg/10 mL and 10 mg/2 mL, supplied in colorless glass vials
Indication: For the treatment of primary hemophagocytic lymphohistiocytosis (HLH)
Due Date: 11/2/2018

RECOMMENDATION:

Approval is recommended from a facility perspective.

SUMMARY

Novimmune SA submitted this new Biological License Application (BLA) dated March 20, 2018. Emapalumab drug product is a concentrate for solution for infusion which is presented as a clear or slightly opalescent, colorless to slightly yellow liquid and free from visible particles. Emapalumab is manufactured in two presentations, 2 mL and 10 mL, each presentation containing 5 mg/mL of emapalumab (b) (4) As part of this BLA there were two pre-license inspections (PLI) conducted which were the following:

- (b) (4)
- Patheon Italia S.p.A., (FEI 3004110157) – Drug Product (DP) Manufacturing Inspection, as part of a cGMP surveillance inspection conducted by District. Inspection occured 9/10-21/2018 – Outcome classified as VAI (CMS # 243391)

The scope of this review is primarily for equipment and facilities. From a facility perspective approval is recommended.

ASSESSMENT

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Adequate information of the facilities, equipment were provided for Emapalumab DS and DP manufacturing and therefore approval is recommended from a facility perspective.

Ziyang Su -S

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Ziyang Su, Ph.D.
Chemist
OPF Division of Inspectional Assessment Branch 1

Zhihao Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment Branch 1

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

Date: November 2, 2018
STN: 761107/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologics License Application
Applicant: Novimmune S.A.
Facilities: (b) (4)
Product: GAMIFANT®(emapalumab)
Dosage: solution for injection/ infusion (10 mg/2 mL, 50 mg/10 mL)
Indication: Treatment for primary hemophagocytic lymphohistiocytosis
Action Date: November 20, 2018

Recommendation: The drug product section of this BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

Introduction

Novimmune S.A. has submitted a biological license application (BLA) for the approval of GAMIFANT® (emapalumab). Emapalumab is a fully human anti-interferon gamma (IFNγ) monoclonal antibody and is proposed for the treatment of patients with primary haemophagocytic lymphohistiocytosis.

This review covers the manufacturing process for the emapalumab drug product. The drug substance process is covered in a separate review completed by Scott Nichols, Ph.D.

Amendments Reviewed

- Sequence 0006 submitted 08 June 2018
- Sequence 0035 submitted 30 Oct 2018

Assessment

1.14 Labeling

The drug product is supplied in (b) (4) glass vials. The labels instructions direct users to dilute the drug product with 0.9% sodium chloride to a maximum concentration of 2.5 mg/mL, the place the solution into either a (b) (4) syringe or infusion bag. Unused drug product left in in the vial is discarded. The diluted solution is administered immediately or can be stored at 2-8°C for no more than (NMT) 4 hours.

Reviewer comment: Preparation and storage instructions on the label are adequate.

P. Drug Product

P.1 Description and Composition of the Drug Product

The emapalumab drug product is manufactured in two presentations, 2 mL and 10 mL, each containing 5 mg/mL of emapalumab (b) (4). The container is a (b) (4) glass vial with a (b) (4) rubber stopper and aluminum overseal. The container closure system is discussed in further detail in Section 3.2.P.7.

P.2 Pharmaceutical Development

(b) (4)

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Reyes Candau-Chacon

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date:	19 October 2018
To:	Administrative File, 761107/0
From:	Scott Nichols, Ph.D., Reviewer OPQ/OPF/DMA/BIV
Through:	Reyes Candau-Chacon, Ph.D., Quality Assessment Lead OPQ/OPF/DMA/BIV
Subject:	New 351(a) Biologics License Application (BLA)
US License Number:	2082
Applicant:	Novimmune SA
Manufacturing Site:	(b) (4)
Product:	Gamifant (emapalumab, NI-0501)
Dosage:	sterile liquid for intravenous infusion (10 mg/2 mL and 50 mg/10 mL)
Indication:	For treatment of primary hemophagocytic lymphohistiocytosis
Action Date:	November 20, 2018

Conclusion and Approvability Recommendation:

The drug substance portion of BLA 7611107/0, as amended, is recommended for approval from a microbial control and a microbiological product quality perspective. Please refer to the review memo from Dr. Candace Gomez-Broughton for an assessment of sterility assurance and microbiological product quality for the drug product (DP) portions of the BLA.

Product Quality Microbiology Assessment: Drug Substance

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	3/20/2018	Original BLA
0006	6/8/2018	Response to FDA Information Request dated 30 May 2018
0014	8/1/2018	Response to FDA Information Request dated 23 July 2018
0022	9/6/2018	Response to FDA Information Request dated 27 August 2018
0028	10/15/2018	Response to FDA Information Request dated 3 October 2018

Scott Nichols

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Reyes Candau-Chacon

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