CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

OTHER REVIEW(S)

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 20, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	BLA 761094
Drug Name and Strength	Oxervate (cenegermin) ophthalmic solution 0.002%
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dompé farmaceutici S.p.A.
FDA Received Date:	December 22, 2017 and March 5, 2018
OSE RCM #:	2018-56; 2018-795
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Otto L. Townsend, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Oxervate (cenegermin) ophthalmic solution, we reviewed the human factors (HF) validation study report[1] and proposed labels, labeling, and packaging submitted under BLA 761094 for areas of vulnerability that may lead to medication errors. This product is a recombinant form of human nerve growth factor indicated for the treatment of [redacted] (b) (4) neurotrophic keratitis.

1.1 PRODUCT DESCRIPTION

Oxervate is supplied in a weekly carton containing 7 multiple-dose preservative-free vials (one vial used per day), 7 vial adapters (one vial adapter used per day), 42 disposable pipettes (6 pipettes used per day, one pipette every 2 hours), sterile wipes, diary card, and a dose recording card. The user must assemble the vial adapter on top of the vial and attach a new disposable pipette to the vial adapter to draw up solution for each dose of Oxervate.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

The Applicant did not submit the HF study protocol for our review prior to conducting the study and submitting the HF validation study results. Additionally, DMEPA had no prior interactions with the Applicant and did not provide HF comments or guidance prior to the BLA submission.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Drug Product Information/Prescribing Information	A
Background Information Previous HF Reviews	B
Human Factors Validation Study Report	C
Container Label and Carton Labeling Recommendations	D
Product Sample	E
Information Requests Issued During the Review	F

[1] While we refer to the study as "Human Factors Validation Study" in our review, the study did not demonstrate that the user interface supports safe and effective use of the product by intended users.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Labels and Labeling	G

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the HF validation study design and our evaluation findings.

3.1 SUMMARY OF STUDY DESIGN

According to the Applicant, the objective of the HF validation study was to evaluate the safety, effectiveness, and fitness of the device "pipette" for its intended use, for the users and for use environments. The HF validation study included 32 healthy participants, all of whom received training. The study was conducted in Italy.

Participants were asked to assess the procedure and the system after the first and sixth use by scoring the difficulty of use on a 1 (extremely difficult) to 5 (extremely easy) scale. The results reported include the average score. At the end of the first and sixth use, participants were asked to provide subjective feedback on the device use experience; however, individual participant subjective feedback was not provided to the Agency. The Applicant only provided their summary of subjective feedback.

3.2 ASSESSMENT OF STUDY METHODOLOGY

As noted above, the Applicant did not submit the HF validation study protocol for our review prior to conducting the study and submitting the HF validation study results. During our review of the HF validation study results, we noted the underlying study methodology had deficiencies, which raises concerns regarding the utility of the collected data in demonstrating that the user interface supports the safe and effective use of the product. We identified the following deficiencies:

1. Participants were asked to assess tasks by scoring the difficulty using a subjective rating scale of 1 (extremely difficult) to 5 (extremely easy). However, an HF validation study should generally include observational data (e.g., whether the user is able to perform the user task and what difficulties were seen while they were performing user tasks), and subjective data (e.g., feedback from study participants from their own perspective on why they were unable to perform the task successfully).
2. The study was conducted in Italy. For products intended to be marketed in the U.S., the study should be conducted in the U.S. with U.S. residents that represent intended users.

3. It is unclear whether the Instructions for Use (IFU) used in the study was written in English and represented the final, to-be marketed IFU in the U.S.
4. Participants included healthy adults, which were not representative of the intended user population. To simulate real world use, the user group should include participants with neurotrophic keratitis or appropriate surrogates.
5. Caregivers were not included as a user group; however, we expect some patients may have difficulty preparing and administering the product and caregivers may need to administer the product to patients.
6. All participants were trained; however, we do not expect all users will be trained routinely and consistently in real world use so untrained participants should have been included in the study.
7. The Applicant did not provide details on the materials and methods for the training (for example, did participants receive hands-on training vs. an overview of the IFU) that they were validating.
8. The study did not include knowledge assessment questions to test participants' understanding of critical information in the IFU that cannot be observed through performance tasks (e.g., appropriate storage conditions).
9. The Applicant did not provide a proactive and comprehensive use-related risk analysis (URRA) evaluating all tasks the user needs to perform. Thus, we are unable to evaluate the risks associated with all the tasks the user needs to perform.
10. The Applicant did not provide definitions of performance success or failure at each individual task level. Thus, we are unable to determine whether we agree with the Applicant's definitions of performance success or failure.
11. The Applicant did not provide the moderator script. Thus, we are unable to determine whether the moderator script contains any leading statements that may bias the study results.
12. Part of the study report is written in Italian. The Applicant should have provided the entire study report in English because we cannot translate or evaluate portions of the report that are not in English.

3.3 RESULTS AND ANALYSIS

Due to the methodology and reporting flaws in the study design noted above, a full analysis could not be completed by DMEPA. Additionally, the data we could evaluate are insufficient to support a determination of whether the user interface supports the safe and effective use of the product by intended users for intended uses and environments.

3.4 PRODUCT DESIGN, LABELS AND LABELING

We evaluated the proposed packaging, labels, and labeling. Table 2 below includes our identified medication error issues, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Transplant and Ophthalmology (DTOP)			
Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1	Throughout the PI, the product strength is presented as 20 µg/mL.	The strength of ophthalmic products is usually expressed as a percentage (e.g., 0.002%). Also, the abbreviation for micrograms, 'µg', has been identified on the Institute for Safe Medication Practices (ISMP's) list of error-prone abbreviations. 'µg' may be mistaken for 'mg', which could lead to dosing errors.[2]	We defer to the Office of Pharmaceutical Quality (OPQ) on the appropriateness of the strength presentation (mcg/mL vs. %). If OPQ determines that the strength presentation should be expressed as a percentage, the strength expression should be revised accordingly throughout labeling. If OPQ determines that the strength should be expressed as mcg/mL, we recommend the strength expression be revised from 'µg/mL' to read 'mcg/mL'.
2	Throughout the PI in sections that mention both 'Storage at the Pharmacy' and 'Storage by the Patient', the lower	For clarity, it is important to label all temperature ranges with appropriate units so that the	Revise section 16 by adding the unit of measure, '°C' after the number '-20' within the Celsius/Centigrade temperature range and the unit of measure '°F' after the

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 04 10]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

	numerals of the temperature storage range do not contain the corresponding abbreviation for Celsius/Centigrade and Fahrenheit.	product can be stored appropriately.	number '-4' within the Fahrenheit temperature range. For example, "(-20°C ± 5°C, or -4°F ± 9°F)" <u>Storage by the Patient:</u> Add the unit of measurement, '°C' after the number 2 within the Celsius/Centigrade temperature range and the unit of measurement, '°F' after the number 36 within the Fahrenheit temperature range. For example, "2°C to 8 °C (36°F to 46 °F)"
Highlights of Prescribing Information			
1	Within the Dosage and Administration section, the word 'eight' is spelled out rather than expressed as the Arabic numeral '8'. All other number presentations in this section are in Arabic numerical form (i.e. 1, 2, 3).	We recommend expressing numbers in a uniform way to improve readability.	Change the word 'eight' to the Arabic numeral '8'. For example: "Treatment should be continued for 8 weeks."
Full Prescribing Information			
1	Within section 2.2, Recommended Dosage and Dose Administration, the word 'eight' is spelled out rather than expressed as the Arabic numeral '8'. All other number presentations in this section are in Arabic numerical form (i.e. 1, 2, 3).	We recommend expressing numbers in a uniform way to improve readability.	Change the word 'eight' to the numerical expression '8'. For example, "Treatment should be continued for 8 weeks."

2	The NDC is denoted with a placeholder in the *How Supplied* section	We generally ask sponsors to submit the full NDC to allow us to evaluate the NDC from a medication error perspective.	Recommend the Applicant submit the PI with the actual NDC.
Instructions for Use (IFU)			
1	Step 14 instructs the user that 'drop is dropped into the conjunctival fornix.'	A lay user may not know what a 'conjunctival fornix' is and may be confused by this technical terminology, resulting in them administering the drug incorrectly.	Consider changing 'conjunctival fornix' to language that is better understood by a layperson, such as, 'inside your lower lid'. We defer to the Division of Medical Policy Programs' Patient Labeling Team for the appropriate language.
Carton Labeling			
(b) (4)			

		(b) (4)	

4 CONCLUSION AND RECOMMENDATIONS

We find that the human factors (HF) validation study results are not acceptable. There is insufficient data to conclude that the user interface supports the safe and effective use of the product.

We advise that the Applicant conduct another HF study prior to approval of the BLA, taking into consideration the study methodology concerns identified below. However, we defer to the Review Division for determination of whether the benefits of introducing this product with its existing user interface outweighs the risk for use errors that can result in improper dosing. We provide letter ready comments in Section 5 below that can be sent to the Applicant.

Furthermore, our evaluation of the proposed user interface, labels and labeling identified areas of vulnerability that may lead to medication errors. We collaborated with the Office of Biologic Products to provide recommendations to address the identified issues with the container label and carton labeling (see Appendix D, Table 4) and provided our recommendations to the Division for consideration.

5 RECOMMENDATIONS FOR DOMPÉ FARMACEUTICI S.P.A.

You did not submit the human factors (HF) validation study protocol for our review prior to conducting the study and submitting the HF validation study results. During our review of the HF validation study results, we identified several deficiencies with the study methodology and determined that the testing conditions and user groups are not representative of expected use. Thus, inadequate data regarding the safe and effective use of this product by intended users was collected (See HF Validation Study Methodology Deficiencies below). We were unable to complete a full analysis of the study results data and the results are not generalizable to real-world use of this product in the United States. You will need to conduct another HF study taking into consideration the study methodology deficiencies identified below. In addition, our evaluation of the proposed user interface, labels and labeling identified areas of vulnerability that may lead to medication errors (See User Interface, Label and Labeling Deficiencies below). Ensure our recommendations are implemented as part of the user interface prior to conducting another HF validation study.

HF Validation Study Methodology Deficiencies

1. Participants were asked to assess tasks by scoring the difficulty using a subjective rating scale of 1 (extremely difficult) to 5 (extremely easy). However, an HF validation study should generally include observational data (e.g., whether the user is able to perform

the user task and what difficulties were seen while they were performing user tasks), and subjective data (e.g., open ended feedback from study participants from their own perspective on why they were unable to perform the task successfully).

2. The study was conducted in Italy. For products intended to be marketed in the U.S., the study should be conducted in the U.S. with U.S. residents that represent intended users.
3. It is unclear whether the Instructions for Use (IFU) used in the study were written in English and represent the final, to-be marketed IFU in the U.S.
4. Participants included healthy adults, which were not representative of the intended user population. To simulate real world use, the user group should include participants with neurotrophic keratitis or appropriate surrogates. If you choose surrogates, please obtain the Agency's concurrence with regards to the potential surrogates that you plan to use in your study prior to conducting your study.
5. Caregivers were not included as a user group; however, we expect some patients may have difficulty preparing and administering the product and caregivers may need to administer the product to patients. Thus, caregivers should be included as a separate user group (e.g. 15 caregivers).
6. All participants were trained; however, we do not expect all users will be trained routinely and consistently in real world use so untrained participants should not have been included in the study. Thus, we expect separate user groups of 15 untrained patients and 15 untrained caregivers.
7. Provide details on the materials and methods for the training (for example, will participants receive hands-on training vs. an overview of the IFU) that you are validating. We consider training to be a component of the product user interface. Discuss how you plan to evaluate training in your study.
8. The study did not include knowledge assessment questions to test participants' understanding of critical information in the IFU that cannot be observed through performance tasks (e.g., appropriate storage conditions). Thus, include knowledge assessment questions to test participants' understanding of all critical information in the IFU, and evaluate the subjective responses that you receive in this assessment.
9. Provide definitions of performance success or failure at each individual task level so that we can determine whether we agree with your definitions.
10. Provide the moderator script detailing the planned interactions between the moderator and participant so we can determine whether the moderator script contains any leading statements that may bias the study results.
11. Part of the study report is written in Italian. Thus, ensure the entire study report is in English because we cannot translate or evaluate the report if it is not written in English.

Additionally, ensure that your study report includes a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should

include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The risk analysis can be used to inform the design of the HF validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

The following items will facilitate an efficient review of your HF study protocol:

- A summary of preliminary analyses and evaluations, including formative studies;
    - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product
- Detailed HF validation study protocol to include the following elements:
    - Description of intended product users, uses, use environments, and training (if applicable) for commercial product
    - Graphical depiction and written description of product user interface
    - Summary of known use problems with previous models or similar products
    - User task selection, categorization (e.g., critical) and prioritization
    - Validation testing details
        - Objective(s)
        - Type of testing (simulated or actual use)
        - Test environment and conditions of use
        - Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
        - Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
        - User tasks and use scenarios that will be studied
        - Description of data to be collected and methods for documenting observations and interview responses
        - Methods for root cause analysis of all use errors, difficulties, close calls
        - Definition of performance success and performance failure

    - Moderator script
- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
- Five intend-to-market samples of product that will be tested in the HF validation study

Place the requested information in eCTD Section 5.3.5.4 – Other study reports and related information.

Guidance on HF procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

User Interface, Labels and Labeling Deficiencies

1. In addition, our evaluation of the proposed user interface, labels and labeling identified areas of vulnerability that may lead to medication errors. We determined use of the pipette may result in difficulty in product administration and/or improper dosing. According to Step 12 of the IFU, *Air bubbles may cause blockage and prevent the pipette from filling properly (especially at first withdrawal).* However, it is difficult to draw up solution into the pipette

without air bubbles. Additionally, we expect users with low/blurred vision may have difficulty determining whether air bubbles are present in the pipette prior to administering the product, especially because Oxervate is a clear, colorless solution. Thus, we are concerned that air bubbles being formed in the pipette as the user draws up the solution may result in an underdose.

2. Furthermore, the IFU instructs users to form a single drop with the pipette; however, the pipette holds more than one drop of volume. It is difficult to form a single drop using the pipette. When attempting to form a single drop, the entire solution can be released from the pipette, resulting in most of the solution missing the eye completely. Thus, we are concerned users may miss therapy or administer an underdose and it is unclear whether there is enough overfill in the vial to account for multiple missed doses throughout the day. Consider design modifications or alternative design options for the delivery of Oxervate to minimize the risk for underdose.

Ensure our recommendations are implemented prior to conducting the HF validation study.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Oxervate (cenegermin) Ophthalmic Solution that Dompé farmaceutici S.p.A. submitted on December 22, 2017 and March 5, 2018.

Table 3. Relevant Product Information for Oxervate	
Initial Approval Date	N/A
Active Ingredient	Cenegermin
Indication	[redacted] (b) (4) neurotrophic keratitis
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.002%
Dose and Frequency	One drop in the affected eye 6 times per day (every 2 hours) for 8 weeks, maximum daily dose per eye is 6 drops
How Supplied	Vial with delivery system for instillation
Storage	Long term storage at T= -20°C; [redacted] (b) (4) Storage at room temperature prior to use
Container Closure	Multi-dose [redacted] (b) (4) vials closed with a rubber stopper and an aluminum seal with a polypropylene flip-off.
Intended Users	Patients, caregivers
Intended Use Environment	Outpatient (home)

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On May 21, 2018, we searched the L:drive and AIMS using the terms, Oxervate and Cenegermin to identify reviews previously performed by DMEPA.

B.1.2 Results

Our search did not identify any reviews relevant to the current review.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\cdsesub1\evsprod\bla761094\0002\m3\32-body-data\32p-drug-prod\oxervate-0020mgmleyedrops\32p2-pharm-dev\pharmaceutical-development-11.pdf

APPENDIX D. CONTAINER LABEL AND CARTON LABELING RECOMMENDATION

The identified issues and recommendations included in Table 4 were combined with those from OBP and provided to the Division for their consideration.

Table 4: Identified Issues and Recommendations for Dompé farmaceutici S.p.A			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Product Design-the following provides our heuristic and expert evaluation of the samples that were submitted			
1.	Use of pipette may result in difficulty administering the product	According to Step 12 of the submitted IFU, *Air bubbles may cause blockage and prevent the pipette from filling properly (especially at first withdrawal).* However, a) Our evaluation of the samples indicate it is difficult to draw up solution into the pipette without air bubbles. b) We expect users with low/blurred vision may have difficulty determining whether air bubbles are present in the pipette prior to administering the product, especially because Oxervate is a clear, colorless solution. Thus, we are concerned that air bubbles being formed in the	Consider design modifications with the device constituent part or other risk mitigation strategies to minimize air bubbles and blockage with the pipette that may lead to difficulties in administration or negatively impact proper dosing

		pipette as the user draws up the solution may lead to difficulties in administration and/or may impact proper dosing.	
2	The use of the pipette may result in omission of therapy	The IFU instructs users to form a single drop with the pipette; however, the pipette holds a volume greater than one drop. When evaluating the submitted samples, it was difficult to form a single drop using the pipette. When attempting to form a single drop, the entire solution can be released from the pipette, resulting in most of the solution missing the eye completely or dribbling out of the eye due to the larger volume. If this were to occur repeatedly, it is unclear whether there is enough overfill in the vial to account for this. If there is insufficient product, this may lead to dose omissions later in the day or later in the course of therapy (e.g., if a user opens another vial intended for the next day's administration).	Consider design modifications with the device constituent part or other risk mitigation strategies to minimize the risk for omission of therapy
Container Labels			
1.	The vial label is missing the name of the	The manufacturer/packer or distributor of the drug is part of the minimum information that is	Add the name of the manufacturer/packer or distributor of the drug on the vial label. 21 CFR 201.10(i) outlines the minimum requirements for small labels (i.e. vials), which

	manufacturer/packer or distributor of the drug.	required to be on small labels (i.e. vials) and is important for product distinction.	includes the requirement for the name of the manufacturer/packer or distributor.
2.	Expiration date on the vial label does not specify the date format to be displayed.	If the expiration date is not clearly expressed, users can be confused and use expired product (administration errors).[3]	We recommend that the expiration date appear in YYYY-MM format if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month for clarity. We also recommend that a hyphen or a space be used to separate the portions of the expiration date for improved readability.
Carton Labeling			
1.	Expiration date on the carton labeling does not specify the date format to be displayed.	If the expiration date is not clearly expressed, users can be confused and use expired product (administration errors).[3]	We recommend that the expiration date appear in YYYY-MM format if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month for clarity. We also recommend that a hyphen or a space be used to separate the portions of the expiration date for improved readability.
Packaging- Kit Box Labeling			
1.	The Principal Display Panel (PDP) of the kit box does not contain the proper name or product strength.	Per 21 CFR 610.61 the proper name and drug strength shall be included on the PDP to reduce the likelihood of product selection errors.	Add the proper name (cenegermin), the product strength (20 mcg/mL) and the dosage form (ophthalmic solution) to the PDP of the kit box.
2.	The NDC is missing from the PDP.	The NDC is traditionally used by healthcare providers to check the	Recommend adding the NDC to the PDP.

[3] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

		correct product, strength, and formulation.[4]	
3.	Net quantity is missing from the PDP.	Missing net quantity statement may result in confusion.	Add the net quantity statement to the PDP.[5]
4.	Package type term is missing.	The package type term is needed to identify how the medication should be safely handled and used.[6]	Add the package type term to the PDP.
5.	[redacted]		(b) (4)

[4] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[5] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[6] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

		(b) (4)	

APPENDIX E. REVIEW OF PRODUCT SAMPLE

We received Oxervate product samples for evaluation. Upon our evaluation, we found that it is difficult to draw up solution into the pipette without air bubbles. Furthermore, we expect users with low/blurred vision may have difficulty determining whether air bubbles are present in the pipette prior to administering the product, especially because Oxervate is a clear, colorless solution. We are concerned that air bubbles in the pipette may result in an underdose.

Additionally, we determined the IFU instructs users to form a single drop with the pipette; however, the pipette holds more than one drop of volume. Upon our evaluation, we found that it is difficult to form a single drop with the pipette. When attempting to form a single drop, the entire solution can be released from the pipette, resulting in most of the solution missing the eye completely. Thus, we are concerned users may miss therapy or administer an underdose and it is unclear whether there is enough overfill in the vial to account for multiple missed doses throughout the day.

Based on our evaluation of the product sample, we recommend the Applicant evaluate alternative designs for the administration of Oxervate to minimize the risk for medication errors.

APPENDIX F. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We sent an information request on May 30, 2018 and the Applicant responded on June 5, 2018:

\\cdsesub1\evsprod\bla761094\0039\m1\us\111-info-amend\1-11-1-quality-information-amendment.pdf

We determined the Applicant's response is inadequate (See Table 4 above).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[7] along with postmarket medication error data, we reviewed the following Oxervate (cenegermin) labels and labeling submitted by Dompe farmaceutici S.p.A. on December 22, 2017 and March 5, 2018.

- Container label
- Carton labeling
- Kit Box labeling
- Diary Card
- Dose Recording Card

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Prescribing Information-accessible in EDR via: \\cdsesub1\evsprod\bla761094\0016\m1\us\114-labeling\114a-draft-label\uspi.docx
- Patient Information Leaflet including Instructions for Use (IFU)- accessible in EDR via: \\cdsesub1\evsprod\bla761094\0016\m1\us\114-labeling\114a-draft-label\patient-leaflet.pdf

G.2 Label and Labeling Images

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NASIM N ROOSTA
07/20/2018

OTTO L TOWNSEND on behalf of MILLIE B SHAH
07/20/2018

OTTO L TOWNSEND
07/20/2018

QUYNHNHU T NGUYEN
07/23/2018

IRENE Z CHAN
07/23/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

Memorandum of Review for Immunogenicity Assays

Original BLA:	761094
Primary reviewer:	Merry Christie, Ph.D. Joao Pedras-Vasconcelos, Ph.D.
Secondary Reviewer:	Maria Cecilia Tami, Ph.D.
Tertiary Reviewer:	Susan Kirshner, Ph.D.
Product:	Oxervate/Cenegermin (recombinant human nerve growth factor; rhNGF),
OBP Name:	RPRO P01138 (NGF_HUMAN) Human Nerve Growth Factor [cenegermin]
Indication:	Treatment of (b) (4) neurotrophic keratitis (NK)
Route of Admin:	Topical (ophthalmic)
Dose Regimen:	One drop in affect eye(s) 6 times a day
Applicant:	Dompé farmaceutici S.p.A.
Clinical Division:	OAP/DTOP
Received Date:	December 22, 2017
Target Date:	July 6, 2018
PDUFA Date:	August 22, 2018

Recommendation:

The validation of the assay used to test clinical samples for the presence of ADA is suboptimal based on the data submitted in validation report *M13013BPL hNGF: Validation of an Analytical Method for the Determination of Binding Antibodies in Human Serum*. The assay cut point was not robustly established. However, the data provided indicate that the assay can accurately detect ADAs levels lower than 100 ng/ml, enabling detection of low levels of antibody concentrations associated with clinical events. No ant-drug antibodies (ADA) were detected using the current assay in any patient evaluated. For the reasons described, there is some level of uncertainty regarding the immunogenicity assessment of clinical samples for the presence of anti-drug antibodies (ADA). However, at this time, there is no evidence of ADA potentially affecting cenegermin safety and efficacy profile and therefore, no additional assay validation data are requested. Additional assay validation, including the establishment of a robust assay cut-point, will be required should the applicant change presentation or

clinical indication. These expectations will be conveyed to the Sponsor in an advice letter that will be sent after an official action is taken on this application. Labelling changes are recommended to section (b) (4)

(b) (4)

Report M13013BPL hNGF: Validation of an Analytical Method for the Determination of Binding Antibodies in Human Serum

Reviewer Comment:
Immunogenicity testing and assay validation were conducted at (b) (4) *The Applicant provided the validation reports for a binding assay. Validation reports for confirmatory and neutralizing assays were not submitted, which is acceptable in the absence of detected ADA. The applicant based their validation on the 2009 Immunogenicity draft guidance, as the assay was developed between 2012-2014.*

Binding Assay

A sandwich ELISA assay is used to detect ADA in human patient serum. The assay uses cenergermin (b) (4) (DS reference standard lots RS0712 and RS1213). The positive control is a commercially available rabbit anti-human NGF polyclonal (Abcam; lots GR22181S-5 and GR128714S-1), which is diluted in commercially available human serum (b) (4) For detection, the assay uses commercially available peroxidase-conjugated goat anti-rabbit IgG and goat anti-human IgG antibodies (b) (4) for detection of the positive control and test samples, respectively. Tetramethylbenzidine (TMB) is used as detection reagent and sulfuric acid as stop reagent. Results are obtained by OD reading at 450nm.

Reviewer comment:
Detection uses mixed goat anti-rabbit and goat anti-human polyclonal antisera. No wells coated with human Ig as positive controls were included during validation to ensure that the anti- rabbit/anti-human cocktail can detect human antibodies. This
Assay control should normally be included to rule out false negative results. However, positive controls were used throughout assay validation, so this concern was mitigated.

Cut Point

- Methodology: Cut point was defined as the level of response at or above which a sample is define to be positive, and below which a sample is defined to be negative with a false positive rate of 5%. The cut point was calculated as Mean + 1.645 x SD (upper 95% confidence limit) using 25 different healthy sera undiluted or diluted 1:50 and analyzed in independent runs by 2 analysts (one run for each analyst).
- Results: The fixed cut point was calculated as 0.393.

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Reviewer comment:
The applicant tested 25 healthy sera undiluted and at 1:50 dilution analyzed in duplicate by two analysts for cut point determination. This approach is insufficient to establish a robust assay cut point. The 2016 and 2009 draft guidances for immunogenicity assays development and validation recommend that the assay cut point should be determined statistically with a minimum of 50 samples tested on at least 3 different days by at least two analysts using suitable statistical methods. The Sponsor established a fixed cut point using the formula Mean + 1.645 x SD (upper 95% confidence limit). This approach requires that the data are normally distributed. However, the Sponsor did not provide a statistical evaluation of the data to support the adequacy of the approach used to establish the assay cut-point. In addition, cut point was determined using commercial healthy sera and was not reassessed with in study pre-treatment samples. Further, no outlier analysis was performed other than visual assessment of the raw data. Overall, the approach to cut point assessment is weak.

The applicant states that in some cases the cut-point may need to be determined using pre-study samples, and/or may need a correction factor (floating cut-point). However, it is unclear whether these approaches were applied as the validation report does not include data showing cut point determination using pre-study samples or the calculation of a floating cut point. If the product were parenterally administered, the applicant would be requested to provide cutpoint assessment using pre-study samples. However, as the product is topical, shows minimal systemic absorption, and the product is these data will not be requested.

Positive & Negative Controls

Positive control samples (polyclonal rabbit anti-human NGF; referred to as surrogate standards by the validation report) were prepared as summarized in the following table:

Surrogate Standard	Nominal Concentration [ng/mL]	Dilution Factor
Std 1(proposed ULOQ)	125	10.0
Std 2	62.5	2.0
Std 3	31.25	2.0
Std 4	15.625	2.0
Std 5	7.813	2.0
Std 6	3.906	2.0
Std 7 (proposed LLOQ)	1.953	2.0
Std 8	0	-

For a negative control, the applicant used commercially available human serum (b) (4) , but information on the composition of the pooled negative control was not provided in the validation report.

Accuracy and Limits of Quantification of Positive Controls

- Methodology: Independent positive control solutions were prepared in duplicate in pooled human serum as summarized in the table above. Data were collected for a total of 34 runs.
- Results:
  - Accuracy was 83.2-119.7% (excluding the lowest and highest dilutions) with a correlation coefficient of ≥0.994
  - Limits of Quantification:
    - Lower limit of quantification (LLOQ) is listed at 1.953 ng/mL with accuracies of 83.7-123.3%
    - Upper limit of quantification (ULOQ) is listed at 125 ng/mL with accuracies of 85.0-108.0%.
    -

Reviewer comment:
The accuracy of the assay is acceptable.

Sensitivity

- Methodology: To determine sensitivity, the positive control samples (1.953-125 ng/mL) were run in duplicate. Sensitivity of the assay was calculated (interpolated) as the lowest positive signal at or above the cut point

- Results: Sensitivity was listed at <500 ng/mL.

28	05-Jun-2013

Reviewer Comment:
The assay uses the Abcan commercial rabbit anti-hNGF as the system suitability positive control. The applicant tested two different lots (A and B) of commercial rabbit anti-hNGF positive control in their assessment. The applicant lists the assay sensitivity at <500ng/ml, based on the recommendations of the 2009 FDA draft guidance for immunogenicity assays development and validation. However, the data provided indicate that the assay sensitivity is at or below 4ng/ml. The assay sensitivity is adequate and higher than the recommended sensitivity of 100 ng/ml, the lowest concentration of ADA that may be associated with clinical events.

Quality Control (QC) Samples
Independent QC samples are prepared using the positive control as summarized in the following table:

Standard	Nominal Concentration [ng/mL]	Final Dilution Factor
QC1	100.000	12.5
QC2	62.500	1.6
QC3	20.161	3.1
QC4	6.504	3.1
QC5	2.098	3.1

Reviewer comment:
The applicant used 5 different QC standards during validation, which is higher than the typical HQC, MQC and LQC. QC5 (LQC) is set at ~2.1ng/ml which is below the estimated sensitivity of 3.9ng/ml from table 3, and thus this QC standard is not informative of assay performance. QC4 is set at 3X the calculated LLQC of the assay and is adequate to monitor consistent assay performance.

Minimal required dilution (MRD)

- Methodology: The MRD of 1:50 dilution was determined using 25 individual human serum samples. The MRD was defined as the dilution factor of negative serum samples that yields a signal close to the signal of non-specific binding

(below LLOQ). The acceptance criterion was that the MRD of serum samples should not exceed 1:100.

- Results: MRD is between 1:50 and 1:150

Reviewer comment: the MRD of 1:50 is acceptable. It is unclear if the applicant ever used 1:150 in their sample assessment.

Recovery/selectivity

- Methodology: Recovery was determined using 10 individual batches of human serum spiked with positive control antibody at the lowest QC concentration (QC5 at 2.098 ng/mL).
- Results: The results indicate
  - Accuracies of 75.2-119.9%
  - Precision of 1.8-15.4%
  - CV of 1.0-15.4%

Reviewer comment: The applicant chose QC5 to assess assay selectivity/recovery. Based on the sensitivity data (Table 3 of this memo), the QC5 standard falls below the calculated fixed cut-point of the assay. Therefore, the relevance of these data is unclear.

Specificity & Drug Tolerance

- Methodology: Specificity, selectivity, and drug tolerance were assessed by immunodepletion. Pooled human serum was pre-incubated for 2 hours at 25°C with or without the addition of DS Reference Standard (RS) at 14 serial dilutions between 2.4-20,000 ng/mL or 12-100,000 ng/mL. Then, samples were spiked with ULOQ (125 ng/mL) and LLOQ (1.953 ng/mL) derived from the positive control linearity curve. The acceptance criterion was if the difference in OD between immunodepleted and not immunodepleted samples is $\geq$ 30%, the sample is positive. Otherwise, it is negative.

- Results: Two batches of DS RS were used to test specificity, selectivity, and drug tolerance. Each batch was diluted to a different concentration range for spiking.
  - DS RS (diluted to 2.4-20,000 ng/mL): 39.1 ng/mL of DS RS masked the positive signal of the ULOQ. 625-2500 ng/mL of DS RS masked the LLOQ signal.
  - DS RS (diluted to 12-100,000 ng/mL): 12.2 ng/mL of DS RS masked the ULOQ and LLOQ signal.

Reviewer Comment:
The applicant selected a LLOQ of 1.953 ng/ml that results in OD values (0.344) below the assay cut-point (0.393). QC4 (6.5 ng/ml) is a more adequate standard for the assessment of tolerance. Drug tolerance is insufficiently established at the low end of the assay. However, PK analyses showed that ocularly administered rhNGF is not systemically absorbed. Therefore, the levels of rhNGF in serum should be negligible, and drug interference is not expected. Thus, no further assessment will be requested.

Precision
To determine assay precision, the applicant analyzed QC1-QC5 across 32 runs:
Inter-assay precision: CV 0.6-19.7%
Intra-assay precision: CV 5.9-15.9 (run 1)

Reviewer Comment: The inter-assay and intra-assay precision < 20% and are acceptable.

Sample stability

- Methodology: QCs were analyzed after storage at the following conditions:
  - 3 freeze-thaw cycles (-80°C for at least 12 hours/thawing at room temperature)
  - Room temperature for at least 4 hours
  - 4°C for at least 4 hours
  - -80°C for 4, 8, 12, and 16 weeks
  - -20°C for 4, 8, 16, 32, and 48 weeks

- Results: Compared to fresh samples, QCs stored using the conditions listed above had the following accuracy, and precision:
  - Accuracy: 81.3-119.9%
  - Precision: 0.7-16.0%

Reviewer comment: *The accuracy and precision results support that the QCs samples remain stable when stored at the temperature and time conditions listed above and after 3 freeze-thaw cycles and that these conditions do not significantly impact the results of the assay.*

Overall assay assessment:
The validation of the assay used to test clinical samples for the presence of ADA is suboptimal based on the data submitted in validation report *M13013BPL hNGF: Validation of an Analytical Method for the Determination of Binding Antibodies in Human Serum*. The assay cut point was not robustly established. However, the data provided indicate that the assay can accurately detect ADAs levels lower than 100 ng/ml, enabling detection of low levels of antibody concentrations associated with clinical events. No anti-drug antibodies (ADA) were detected using the current assay in any patient evaluated. For the reasons described, there is some level of uncertainty regarding the immunogenicity assessment of clinical samples for the presence of anti-drug antibodies (ADA). However, currently, there is no evidence of ADA potentially affecting cenegermin safety and efficacy profile and therefore, no additional assay validation data are requested. Additional assay validation, including the establishment of a robust assay cut-point, will be required should the applicant change presentation or clinical indication. These expectations will be conveyed to the Sponsor in an advice letter that will be sent after an official action is taken on this application.

Immunogenicity assessment of Clinical samples

Eight clinical trials were conducted to study safety and efficacy of cenegermin, see table below. Immunogenicity was assessed in the four clinical trials highlighted in yellow.

Table 1: Completed clinical Studies with rhNGF

Code Phase Location	Key objectives	Countries	Group	Doses	Subjects randomized/ uncontrolled or rescue treated[a]	Safety database for rhNGF[b]
NGF0112 Phase I Module 5.3.3.1	Safety, PK, dose escalation (formulation without methionine)	Switzerland, UK	Healthy volunteers	0.5-5 µg/ml	6	58
				20 µg/ml	21	
				60-180 µg/ml	31	
				Vehicle	16	
				Total	**74**	
NGF0212 Phase I segment Module 5.3.5.1	Safety, PK, dose escalation (formulation without methionine)	Italy, France, UK, Germany, Spain, Hungary, Portugal, Belgium, Poland	Stage 2-3 NK	10 µg/ml	7	141
				20 µg/ml	7	
				Vehicle	4	
				Total	**18**	
NGF0212 Phase II segment Module 5.3.5.1	Safety, efficacy, PK, dose-ranging (formulation without methionine)	Italy, France, UK, Germany, Spain, Hungary, Portugal, Belgium, Poland	Stage 2-3 NK	10 µg/ml	52/10[a]	
				20 µg/ml	52/13[a]	
				Vehicle	52	
				Total	**156/23[a]**	
NGF0214 Phase II Module 5.3.5.1	Safety and efficacy	United States	Stage 2-3 NK	20 µg/ml	24/13[a]	36[c]
				Vehicle	24	
				Total	**48/13[a]**	
NGF0213 Phase II Module 5.3.5.4	Supportive for safety only	Austria	Moderate-severe dry eye	4 µg/ml	20	40
				20 µg/ml	20	
				Total	**40**	
NGF0113 Phase I/II Module 5.3.5.4	Supportive for safety only	Italy	Retinitis pigmentosa	60 µg/ml	20	40
				180 µg/ml	20	
				Vehicle	10	
				Total	**50**	
NGF0116 Phase II Module 5.3.5.4	Supportive for safety only	Italy	Post-refractive surgery	20 µg/ml	120	115[d]
				Vehicle	60	
				Total	**180**	

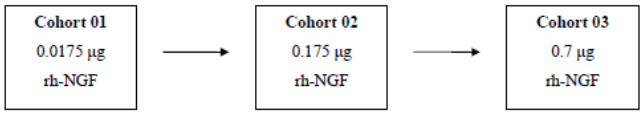
Code Phase Location	Key objectives	Countries	Group	Doses	Subjects randomized/ uncontrolled or rescue treated[a]	Safety database for rhNGF[b]
NGF0216 Phase II Module 5.3.5.4	Supportive for safety only	United States	Dry eye	20 µg/ml	100	100
				Vehicle	50	
				Total	**150**	
NEMO Investigator-initiated Module 5.4	Supportive for safety only	Italy	Retinitis pigmentosa and cystoid macular edema	180 µg/ml	23	23**
				Vehicle	22	
				Total	**45**	
Total # of subjects enrolled in all rhNGF studies to date						**761**
Total # of subjects exposed to rhNGF (any concentration) in all studies to date						**553**
Total # of NK patients exposed to rhNGF (any concentration, with or without methionine)						**177**

Immunogenicity Studies

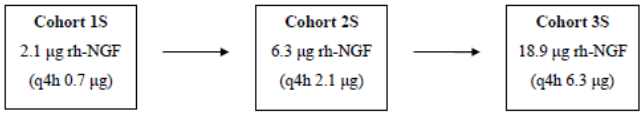
- NGF0112
  - Randomized, double-blind, placebo controlled in healthy adults
  - 73 subjects (57 NGF, 16 placebo); treatment of only one eye (the other eye received placebo)
  - Study design

Figure 9-1: Study Schematic

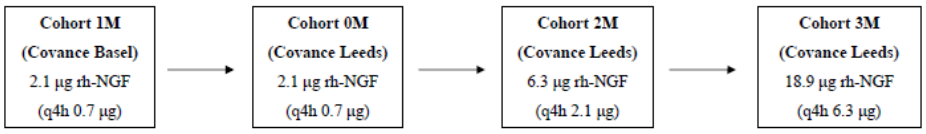
Part 0, Ascending Single Dose (1 treatment day): Covance Basel, N=3,



Part A, Ascending Fractionated Single Dose (1 treatment day): Covance Basel, N=8, 6:2 drug:placebo,



Part B, Ascending Multiple Fractionated Dose (daily fractionated doses on 5 treatment days): Covance Basel and Leeds, N=12, 9:3 drug:placebo,



Abbreviations: N = number of subjects; q4h = once every 4 hours, 3 times a day; rh-NGF = recombinant human nerve growth factor

- Immunogenicity sampling (analyzed at (b) (4)
  - Part 0: none
  - Part A: pre-dose day 1 and follow up on days 30-37
  - Part B: pre-dose day 1 and follow up on days 35-42
- Results:
  - PK: no serum NGF found above limit of quantitation. 4 patients had detectable levels of NGF pre- and post-dose, but no PK data were collected.
  - Immunogenicity: all samples below limit of quantitation (1.953 ng/mL)

- NGF0212
  - Randomized, double-blind, placebo controlled in NK patients
  - 18 subjects (14 NGF, 4 placebo)
  - Study design

Table 2: Phase I Segment of the Study – Cohort 1

PHASE I SEGMENT OF THE STUDY-COHORT 1 (9 patients) 8-Week Randomized, Double-Masked, Controlled Treatment Period		
7	2	
ACTIVE PATIENTS (rhNGF 10 µg/ml)	**VEHICLE CONTROL PATIENTS**	
CH or NCH at Week 8 ⇩ **48-week** follow-up period **CH*:** PFAT, as needed **NCH:** Treatment at discretion of Investigator	**CH*at Week 8** ⇩ **48-week** follow-up period ⇩ PFAT, as needed	**NCH at Week 8** ⇩ **56-week** follow-up period **8-week** uncontrolled treatment period for patients randomized to vehicle control at baseline ⇩ **rhNGF 10 µg/ml** ⇩ **At Week 16** **CH*:** PFAT, as needed **NCH:** Treatment at discretion of Investigator

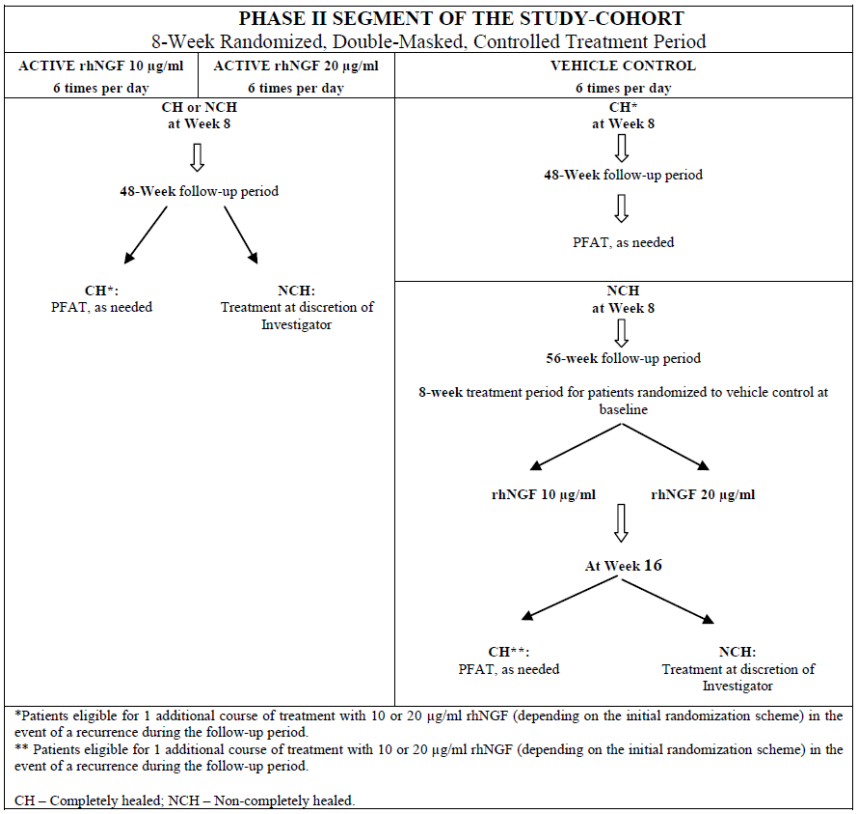
*Patients eligible for 1 additional course of treatment with 10 µg/ml rhNGF in the event of a recurrence during the follow-up period.
**Patients eligible for 1 additional course of treatment with 10 µg/ml rhNGF in the event of a recurrence during the follow-up period.
CH – Completely healed; NCH – Non-completely healed; PFAT – Preservative-free artificial tears

Table 3: Phase I Segment of the Study – Cohort 2

PHASE I SEGMENT OF THE STUDY-COHORT 2 (9 patients) 8-Week Randomized, Double-Masked, Controlled Treatment Period		
7	2	
ACTIVE PATIENTS (rhNGF 20 µg/ml)	**VEHICLE CONTROL PATIENTS**	
CH or NCH at Week 8 ⇩ **48-week** follow-up period **CH*:** PFAT, as needed **NCH:** Treatment at discretion of Investigator	**CH* at Week 8** ⇩ **48-week** follow-up period ⇩ PFAT, as needed	**NCH at Week 8** ⇩ **56-week** follow-up period **8-Week** uncontrolled treatment period for patients randomized to vehicle control at baseline ⇩ **rhNGF 20 µg/ml** ⇩ **At Week 16** **CH*:** PFAT, as needed **NCH:** Treatment at discretion of Investigator

*Patients eligible for 1 additional course of treatment with 20 µg/ml rhNGF in the event of a recurrence during the follow-up period.
**Patients eligible for 1 additional course of treatment with 20 µg/ml rhNGF in the event of a recurrence during the follow-up period.
CH – Completely healed; NCH – Non-completely healed; PFAT – Preservative-free artificial tears

Table 4: Phase II Segment of the Study



- Immunogenicity sampling:
  - Phase I: none
  - Phase II: day 0/pre-dose, week 4, week 8, follow-up/week 12
- Results: pg115 of NGF0212 study report
  - PK:
    - Phase I: No NGF detected in any patient except for one each in the 10 (130 pg/mL at 0.5 hrs post-dose on day 1) and 20 µg/mL (200-1000 pg/mL throughout study; likely due to endogenous levels) groups had NGF levels below LOQ. LOQ is 32 pg/mL
    - Phase II: No NGF detected in any patient except for 3 patients in the 10 ug/ml (~1000-6000 pg/mL at wk 0 and 8; ~250-400 pg/mL throughout; ~150-200 pg/mL throughout) and 2 in the 20 µg/mL (~40-60 pg/mL at day 0, w1, 3; ~225 pg/mL at wk1, 3) groups had NGF levels below LOQ.
  - Immunogenicity (Ph II): no ADA detected

- NGF0113
  - Randomized, double-blind, placebo controlled in NK patients
  - Ph I: 10 subjects (8 NGF, 2 placebo); Ph II: 40 subjects (32 NGF, 8 placebo)
  - Study design: 80 or 180 µg/mL 3x/day for 24 wks

  - Immunogenicity sampling: day 0/pre-dose and wk 24
  - Results:
    - PK was not evaluated
    - Immunogenicity: no ADA detected
- NGF0214
  - Randomized, double-blind, placebo controlled in NK patients
  - 52 subjects (26 NGF, 26 placebo)
  - Study design: 20 µg/mL (methionine-containing) in affected eye(s) 6x/day for 8 wks; patients could also receive an additional course of 8 wks treatment during an uncontrolled treatment period
  - Immunogenicity sampling: Day 0/pre-dose, wk4, wk8, follow-up/wk 12 and/or wk16 or early exit visit
  - Results:
    - PK was not evaluated
    - Immunogenicity: no ADA detected

Reviewer comment:
The applicant stated that anti-drug antibodies (ADA) were not detected in any patients. However, current assay validation is suboptimal based on the data submitted in validation report *M13013BPL hNGF: Validation of an Analytical Method for the Determination of Binding Antibodies in Human Serum*. The assay cut point was not robustly established. However, the data provided indicate that the assay can accurately detect ADAs levels lower than 100 ng/ml, enabling detection of low levels of antibody concentrations associated with clinical events. No anti-drug antibodies (ADA) were detected using the current assay in any patient evaluated. For the reasons described, there is some level of uncertainty regarding the immunogenicity assessment of clinical samples for the presence of anti-drug antibodies (ADA). However, currently, there is no evidence of ADA potentially affecting cenegermin safety and efficacy profile and therefore, no additional assay validation data are requested. Additional assay validation, including the establishment of a robust assay cut-point, will be required should the applicant change presentation or clinical indication. These expectations will be conveyed to the Sponsor in an advice letter that will be sent after an official action is taken on this application. Labelling changes are recommended (b) (4)

(b) (4)


(b) (4)

Joao Pedras Vasconcel

Digitally signed by Joao Pedras Vasconcel
Date: 7/03/2018 03:08:45PM
GUID: 508da6da000265de30f88718141f7e75
Comments: Review was initiatiated by Merry Christie and completed by Joao Pedras Vasconcelos.

Maria Cecilia Tami

Digitally signed by Maria Cecilia Tami
Date: 7/12/2018 02:48:47PM
GUID: 508da6d9000264e1912653dd7f25aae4
Comments: At the time this review memo was uploaded, Susan Kirshner was not available and her name was not added for approval

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 29, 2018
Responsible OND Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	BLA 761094
Product Name and Strength:	Oxervate (cenegermin-bkbj) Ophthalmic Solution 0.002%
Product Type:	Combination Product (Drug-Device)
Applicant/Sponsor Name:	Dompe Farmaceutici S.p.A
FDA Received Date:	February 22, 2018
OSE RCM #:	2018-423
DMEPA Primary Reviewer:	Nasim Roosta, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761094.

1.1 Regulatory History

Dompe Farmaceutici S.p.A was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter[a].

2 ASSESSMENT OF THE NONPROPRIETARY NAME

Cenegermin-xxxx (bkbj)

FDA generated a four-letter suffix, -bkbj. This suffix was evaluated using the principles described in the applicable guidance[b].

We determined that the FDA-generated suffix -bkbj, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. In email correspondence dated June 27, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Transplant and Ophthalmology Products (DTOP) via e-mail on June 27, 2018.

4 CONCLUSION

We find the suffix -bkbj acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to cenegermin-bkbj.

4.1 Recommendation for Dompe Farmaceutici S.p.A

We find the nonproprietary name, cenegermin-bkbj, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, cenegermin-bkbj will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated when you respond to the

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[a] Merchant, L. General Advice Letter for BLA 761094. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 FEB 28.

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NASIM N ROOSTA
06/29/2018

DANIELLE M HARRIS
07/09/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 3, 2018

To: Derek Alberding
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 761094**
OXERVATE™ (cenegermin) ophthalmic solution for topical ophthalmic use

---

OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling submitted for consult on January 24, 2018, for OXERVATE™ (cenegermin) ophthalmic solution for topical ophthalmic use (Oxervate). Our comments are based on the version of the proposed labeling located in Sharepoint and sent to OPDP via email on June 19, 2018. OPDP's comments are provided directly below on the attached marked-up copy of the proposed PI and proposed carton and container labeling.

The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the Patient Package Insert (PPI) and Instructions for Use (IFU) in a joint review under separate cover on July 2, 2018.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
07/03/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 2, 2018
To:	Renata Albrecht, MD Director **Division of Transplant and Ophthalmology Products (DTOP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	OXERVATE (cenegermin)
Dosage Form and Route:	ophthalmic solution for topical ophthalmic use
Application Type/Number:	BLA 761094
Applicant:	Dompe´ Farmaceutici S.p.A.

1 INTRODUCTION

On December 22, 2017, Dompe´ Farmaceutici S.p.A.submitted the final part of their rolling submission for OXERVATE (cenegermin) ophthalmic solution for topical ophthalmic use (BLA 761094) for the Agency's review. The purpose of this submission is to seek approval for OXERVATE (cenegermin) ophthalmic solution for topical ophthalmic use indicated for the treatment of neurotrophic keratitis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on June 19, 2018 for DMPP and OPDP to review the Applicant's proposed PPI and Instructions for Use (IFU) for OXERVATE (cenegermin) ophthalmic solution for topical ophthalmic use.

2 MATERIAL REVIEWED

- Draft OXERVATE (cenegermin) ophthalmic solution for topical ophthalmic use PPI and IFU received on May 31, 2018, and received by DMPP and OPDP on June 19, 2018.
- Draft OXERVATE (cenegermin) ophthalmic solution for topical ophthalmic use Prescribing Information (PI) received on May 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 19, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

15 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
07/02/2018

CARRIE A NEWCOMER
07/02/2018

LASHAWN M GRIFFITHS
07/02/2018

Clinical Inspection Summary

Date **From**	05/17/2018 Cheryl Grandinetti, Pharm.D. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Derek Alberding, RPM Rhea Lloyd, Medical Officer William Boyd, Clinical Team Leader Division of Transplant and Ophthalmology Products
BLA #	761094
Applicant	Dompé Farmaceutici S.p.A.
Drug	Oxervate (cenegermin ophthalmic solution)
NME	Yes
Therapeutic Classification	Recombinant human nerve growth factor
Proposed Indication	Treatment of (b) (4) neurotrophic keratitis.
Consultation Request Date	January 22, 2018
Summary Goal Date	May 18, 2018
Action Goal Date	August 17, 2018
PDUFA Date	August 22, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Giacomina Massaro-Giordano was inspected in support of this NDA. Although regulatory violations were noted at this site, the findings are not likely to significantly impact data reliability. Otherwise, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

The compliance classification of the inspection of Dr. Massaro-Giordano is Voluntary Action Indicated (VAI).

II. BACKGROUND

The Applicant submitted this BLA to support the use of Oxervate (cenegermin ophthalmic solution) for treatment of (b) (4) neurotrophic keratitis. An inspection was requested for the following protocol in support of this application:

NGF0214, "An 8-week phase II, multicenter, randomized, double-masked, vehicle controlled parallel group study with a 24 or 32-week follow-up period to evaluate the efficacy of a formulation containing anti-oxidant of recombinant human nerve growth factor (rhNGF) 20 mcg/ml, eye drops solution versus vehicle containing anti-oxidant in patients with Stage 2 and 3 Neurotrophic Keratitis."

This study took place in 11 sites in the United States, beginning May 1, 2015 and ending August 6, 2016. A total of 48 subjects were randomized.

The primary objective of this study was to evaluate the efficacy of 20 mcg/mL six times a day of recombinant human nerve growth factor (rhNGF) eye drops compared to vehicle in inducing a complete healing of stage 2 (PED) and stage 3 (corneal ulcer) neurotrophic keratitis (NK) as measured by the central reading center evaluating the clinical pictures of corneal fluorescein staining. The primary efficacy endpoint was the percentage of patients achieving complete healing of the PED or corneal ulcer determined by corneal fluorescein staining at 8 weeks as defined by the central reading center evaluating clinical pictures.

The secondary objectives were to assess the duration of complete healing, improvement in visual acuity, improvement in corneal sensitivity, and percentage of patients achieving complete corneal healing defined as complete absence of staining. Secondary efficacy endpoints were:

- Percentage of patients experiencing complete healing of the PED or corneal ulcer determined by corneal fluorescein staining at 8 weeks as measured by the Investigator
- Percentage of patients experiencing complete healing of the PED or corneal ulcer at 4, and 6 weeks as measured by the central reading center evaluating the clinical pictures and Investigator
- Percentage of patients with complete corneal clearing at weeks 4, 6, & 8 defined as grade 0 on the modified Oxford scale
- Mean change in BCDVA from baseline to Week 8
- Percentage of patients that achieve a 15 letter gain in BCDVA at 4 weeks, 6 weeks, 8 weeks
- Percentage of patients that achieve an improvement in corneal sensitivity as measured by the Cochet-Bonnet aesthesiometer at 4, 6 and 8 weeks
- Percentage of patients experiencing deterioration (increase in lesion size ≥ 1mm and/or decrease in BCDVA by >5 ETDRS letters and/or progression in lesion depth to corneal melting or perforation and/or onset of infection) in stage 2 or 3 NK from baseline to Week 8.
- Investigator global evaluation at each time point

Rationale for Site Selection

The site of Dr. Massaro-Giordano was selected because of the site's relatively large enrollment and effects on efficacy.

III. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #6 **Giacomina Massaro-Giordano, M.D.** 51 N 39th Street Philadelphia, PA 19104 phone: 215.662.8038 fax: 215.662.8025	NGF0214 Subjects: 9	2/28/2018- 3/9/2018	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable

Giacomina Massaro-Giordano, M.D.

At this site for Protocol NGF0214, 9 subjects were screened, 9 were enrolled, 1 subject discontinued (early termination), and 8 subjects completed the study. Records reviewed during the inspection included, but were not limited to, all informed consent forms for enrolled subjects; all enrolled subject records and source documents for primary and secondary efficacy endpoint data available at the study site; all enrolled subject records and source documents for eligibility, adverse events (including serious adverse events), and protocol deviations; test article accountability; training records; and regulatory documents.

The secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Of note, the primary efficacy endpoint was based on corneal photographs that were forwarded to a central reading facility for evaluation, and the sites were blinded to the results. Therefore, verification of the primary efficacy endpoint was not feasible during this inspection.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for:

(1) Failure to conduct the investigation in accordance with the signed statement of investigator and investigational plan:

> Specifically, one subject failed to meet the inclusion criteria. At screening, subject (b) (6) had a Schirmer Test measurement of 3 mm for the right eye. According to the protocol, the measurement must be greater than 3 mm for 5 minutes to qualify for the study.
>
> *Reviewer Comment: This subject should not have been included in the study. However, the Schirmer Test measurement for this subject was just outside the range to qualify for the study, so this likely does not have an impact on the results of the study. This protocol violation was reported to the FDA.*

(2) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation:

> Specifically, six subjects at this site missed the following scheduled assessments, or the assessments were performed late:

Subject No.	Visit Week	Missed/Late Scheduled Assessments	OSI Reviewer's comment	Reported to FDA (in CSR)
(b) (6)	D0	Hematology[1] was not done	This assessment was performed late due to inadequate sample	No

[1] Depending on the site, hematology specimens may include hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocyte, eosinophils and basophils) and quantitative platelet count.

			taken on D0. Patient returned 4 days later to have repeat blood draw.	
	W1-W4	Corneal staining/grading was not performed in the fellow eye	The protocol requires this to be done in both the study eye and the non-study eye. Investigator stated that not doing it in the non-study eye was a mistake.	No
	W2	Slit lamp exam was not done in the fellow eye (OS)	The protocol requires this to be done in both the study eye and the non-study eye. Investigator stated that not doing it in the non-study eye was a mistake.	No
	W4	BCDVA was not done in the fellow eye	The protocol requires this to be done in both the study eye and the non-study eye. Investigator stated that not doing it in the non-study eye was a mistake.	No
	W32	Corneal sensitivity and IOP were not done	Subject refused to complete corneal sensitivity and IOP testing for both eyes	No
(b) (6)	D0	Hematology not done	This assessment was not performed due to insufficient blood draw and poor access to veins.	Yes
	D0	Hematology and chemistry[2] were not done	These assessments were performed late. The patient returned approximately 1 week later to have repeat blood draw.	Yes
	D0	Schirmer strips were not saved	N/A	No
	D0	Corneal photos could not be located	The clinical investigator obtained the corneal photos from the Central Reading Center and they are now at the site.	No
	W20	IOP not performed in the fellow eye.	Subject 06-006 refused to complete IOP testing in the fellow eye.	No
	W2	Corneal photography without fluorescein was not done	This assessment was not done by mistake.	No

[2] Depending on the site, clinical chemistry specimens may include blood urea nitrogen (BUN), serum creatinine, BUN/Creatinine ratio, uric acid, cholesterol, triglycerides, albumin, total globulin, A/G ratio, total serum iron, total protein, serum electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium), phosphorus, glucose and the following liver function tests (LFT): serum aspartate transaminase [AST (SGOT)], serum alanine transaminase [ALT (SPGT)], alkaline phosphatase, gamma glutamyl transaminase(GGT), total bilirubin, direct bilirubin, indirect bilirubin and lactate dehydrogenase (LDH).

	End of Treatment (ET)	Schirmer test was not done	The protocol was not followed by mistake.	No
(b) (6)	D0	Hematology not done	This assessment was performed late due to inadequate sample taken on D0. Patient returned approximately 1 week later to have repeat blood draw.	No
	W20	Schirmer test was not done	The protocol was not followed by mistake.	No

Reviewer Comments: The missed or late assessments likely did not have an impact on the efficacy or safety results of the study, especially as none were related to the primary or secondary efficacy endpoints. These missed or late assessments should be considered protocol deviations.

Of note, most of these protocol deviations were not reported to the FDA. In the Clinical Study Report (CSR) synopsis (version 1, dated 04-Oct-2016), the sponsor noted that, in August 2016, they became aware of a monitoring issue with (b) (4) *, the CRO contracted by the sponsor to oversee, manage, and monitor the clinical trial sites.* (b) (4) *performed a root cause analysis and identified inadequate source data verification performed by the study monitor assigned to site 04 (Dr. Ladan Espandar) and site 06 (Dr. Giacomina Massaro-Giordano). The sponsor further noted that they took immediate action to ensure the reliability of all data in the database by further monitoring queries and correcting data from sites 04 and 06 for the study.*

Dr. Massaro-Giordano responded adequately to the inspection findings in a letter dated 03/28/2018.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
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Division of Clinical Compliance Evaluation
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/s/

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05/18/2018

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