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APPLICATION NUMBER:

761094Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY MEMORANDUM

BLA Number	761094 / SDN-7
Link to EDR	EDR Link
Submission Date	12/22/2017
Submission Type	NME Original - Priority
Brand Name	OXERVATE
Generic Name	Cenegermin, Recombinant Human Nerve Growth Factor (rhNGF)
Dosage Form and Strength	20 µg/mL solution, Eye drops
Route of Administration	Topical: ophthalmic solution
Proposed Indication	Treatment of [REDACTED] (b) (4) neurotrophic keratitis.
Applicant	Dompé farmaceutici S.p.A.
OCP Reviewer	Abhay Joshi, Ph.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.

This submission is a 351(a) submission for OXERVATE, which is 20 µg/mL cenegermin ophthalmic solution for topical administration (eye drops). Cenegermin is also known as recombinant human nerve growth factor (rhNGF) and indicated for the treatment of [REDACTED] (b) (4) neurotrophic keratitis. Cenegermin has been granted the *Fast Track*, *Breakthrough Therapy*, and *Orphan* designations by the FDA.

Within the submission, the Applicant has not provided any Clinical Pharmacology information from the proposed to-be-marketed drug product. Specifically, the information on extent of systemic exposure to cenegermin following repeated topical ocular dosing of the proposed to-be-marketed cenegermin eye drops has not been provided by the Applicant. The proposed to-be-marketed drug product is a sterile [REDACTED] (b) (4) ophthalmic solution containing 20 µg/mL of cenegermin and 0.001% w/v of methionine [REDACTED] (b) (4). However, the Clinical Pharmacology information provided by the Applicant in support of this BLA is from the clinical studies that were conducted with the drug product without methionine. Complete details on the available pharmacokinetic (PK) information from the drug product without methionine is summarized in the Clinical Pharmacology review of an IND submission (SDN-33) under IND 115892 (DARRTS Review date 01/30/2017). Given that the Clinical Pharmacology information contained in this submission is not from the proposed to-be-marketed drug product, Clinical Pharmacology review of this information has been not included in this memorandum.

During the development of the proposed drug product and Pre-BLA discussion, FDA requested information with respect to the systemic exposure to cenegermin following repeated topical ocular

dosing of the proposed to-be-marketed cenegermin ophthalmic solution containing methionine. The Applicant has agreed to provide the requested PK information and plans to evaluate the proposed to-be-marketed cenegermin ophthalmic solution in a Phase 1 clinical study; however, the study was not to start prior to Q1 2018. The Applicant will submit the clinical study report from the Phase 1 PK study in June 2018 (General Advice Letter dated, 12/07/2017). Given that the requested PK information in support of this BLA is anticipated to arrive too close to the BLA review goal date, the Clinical Pharmacology Review Team recommends the following Post Marketing Commitment (PMC):

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Time Line
☐ PMR ☒ PMC	Obtain information with respect to the systemic exposure to cenegermin following repeated topical ocular dosing of the proposed to-be-marketed cenegermin ophthalmic solution containing methionine.	The extent of systemic exposures to cenegermin following repeated topical ocular dosing of the proposed to-be-marketed drug product is not known.	3Q 2018 – 1Q 2019

Regarding the Applicant’s proposed labeling, the Clinical Pharmacology Review Team is proposing to include language and or edits to the Applicant’s proposed labeling that convey the lack of clinical PK information from the proposed to-be-marketed information within all the applicable sections.

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/s/

ABHAY JOSHI
05/24/2018

PHILIP M COLANGELO
05/25/2018