CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761094
PDUFA Goal Date	August 22, 2018
OSE RCM #	2018-55
Reviewer Name(s)	Charlotte Jones MD, PhD, MSPH
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	July 10, 2018
Subject	Evaluation of Need for a REMS
Established Name	Oxervate
Trade Name	cenergermin
Name of Applicant	Dompe Farmaceutici
Therapeutic Class	Growth factor
Formulation(s)	Ophthalmic Solution
Dosing Regimen	1 drop 6 times daily for up to 8 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Oxervate (cenergermin) an ophthalmic solution is necessary to ensure the benefits outweigh its risks. Dompe Farmaceutici (Dompe) submitted a Biologics Licensing Application (BLA) 761094 for Oxervate with the proposed indication for treatment of (b) (4) neurotrophic keratitis. The risks associated with drug include eye reactions, eye infection, and a potential risk of progression of malignancy. The applicant did not submit a proposed REMS or risk management plan with this application. The risks associated with Oxervate are localized to the eye, of mild to moderate severity, and Oxervate has demonstrated efficacy for treatment of a vision threatening eye disease, neurotrophic keratitis. DRISK and the Division of Transplant and Ophthalmology Products (DTOP) agree that a REMS is not needed to ensure the benefits of Oxervate outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Oxervate is necessary to ensure the benefits outweigh its risks. Dompe Farmaceutici (Dompe) submitted a Biologics Licensing Application (BLA) [761094] for Oxervate with the proposed indication for the treatment of (b) (4) neurotrophic keratitis. This application is under review in the Division of Transplant and Ophthalmology Products (DTOP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Oxervate, a new molecular entity,[a] is a recombinant human nerve growth factor (rhNGF) proposed for the treatment of (b) (4) neurotrophic keratitis. Oxervate is a 20 µg/ml topical ophthalmic solution to be dropped in the conjunctival sac 6 times a day (at 2-hour intervals for 12 hours). The proposed packaging includes a multidose glass vial with stopper and sterile disinfectant swabs (to clean the vial adapter valve before each use). Treatment should be given for 8 weeks.[b] Oxervate was designated as an orphan medicinal product for the indication of treatment of neurotrophic keratitis; it has been granted breakthrough status and is a priority review. Oxervate was approved by the European Medicines Agency on July 7, 2017.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761094 relevant to this review:

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

- 06/23/2014: Agency designated product as an orphan medicinal product for treatment of neurotrophic keratitis
- 01/12/2015: Agency granted product Fast Track designation
- 5/31/2017: Start of the BLA 76109 rolling submission
- 11/30/2017: Agency granted product Breakthrough Therapy Designation
- 12/22/2017: Final section of dossier for BLA Application number 761094 submitted. PDUFA time clock for review began.[1]
- 05/01/2018: Applicant informed of the need to include sterile wipes in package and agreed to provide these.[2]
- 06/18/16: Applicant informed at Late Cycle Meeting that sterile wipes would need to be co-packaged with sterile disinfectant wipes in the weekly delivery system kit. The Applicant stated that two manufacturers of US-approved and commercially available sterile disinfectant wipes have been identified to be included in the delivery system kit. The Applicant agreed to update the applicable portions of the label.[3]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Neurotrophic Keratitis occurs when the cornea loses or has never had normal corneal sensation. The lack of normal nerve innervation leads to changes in the corneal epithelium and it's normal healing process. This results in nonhealing lesions of the epithelium progressing to corneal ulcerations and can culminate in corneal perforation and vision loss.[4c] The causes of neurotrophic keratitis are many, but the most common is as a sequelae from herpetic viral infection, diabetes, and other processes that have damaged the trigeminal nerve. A more exhaustive list of the etiologies of neurotrophic keratitis is provided in the appendices. Direct data on the number of patients with neurotrophic keratitis is not known, but it is classified as an orphan disease by the FDA and estimated to effect 0.02/10,000 individuals.[5 d]

3.2 Description of Current Treatment Options

Neurotrophic Keratitis is considered one of "the most difficult and challenging ocular diseases that lack a specific treatment".[5] There are no FDA approved treatments. Table 1 identifies the stages of

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

neurotrophic keratitis and the recommended treatments. For stage ii and iii the treatments will result in the closure of the eye and at least temporary loss of vision while healing occurs, if it does.

Table 1 Clinical grading of neurotrophic keratitis and management[5]

Stage	Clinical findings	Treatments
i	Corneal epithelial hyperplasia and irregularity Scattered small facets of dried epithelium (Gaule spots) Superficial punctate keratopathy Rose bengal staining of the inferior conjunctiva increased viscosity of tear mucus	Discontinuation of all topical medications Use of preservative-free artificial tears Treatment of ocular surface-associated diseases
ii	Persistent corneal epithelial defect with smooth and rolled edges	Corneal or scleral therapeutic contact lenses. Surgical tarsorrhaphy
iii	Descemet's membrane folds and stromal swelling Corneal ulcer Corneal perforation Corneal stromal melting	Palpebral spring, botulinum A toxin Cyanoacrylate glue followed by a soft bandage contact lens

4 Benefit Assessment

Two randomized, vehicle controlled, double blinded, superiority studies NGF0212 (NCT01756456) and NGF0214 (NCT02227147) were conducted to determine the efficacy of Oxervate. Study NGF0214 contained the methionine containing rhNGF that is the formulation that will be used in marketing Oxervate and is the pivotal study. Study NGF0212 included two doses of the active product rhNGF at 20 µg/ml and 10 µg/ml and enrolled 156 European subjects. NGF0214 compared 20 µg/ml of Oxervate and placebo and enrolled 48 US subjects. One patient enrolled and was randomized to treatment arm but dropped out before receiving treatment. Study visits occurred at baseline, 1, 2, 3, 4, 6, and 8 weeks during the controlled treatment period. The original protocol defined primary endpoint, which was treated as a key secondary endpoint, was the percentage of subjects with complete healing of the cornea, defined as the lesion size < 0.5 mm as determined by the central reading center. The Agency later determined that the primary endpoint was the percentage of subjects with complete resolution of

corneal staining, defined as 0 mm lesion size and no residual staining as determined by the central reading center. The clinical reviewer identified the findings as both clinically and statistically significant. The Clinical reviewer identified that in the primary endpoint in the trials with the 20 µg/ml dosing, the difference in complete healing at the end of the treatment favored the treatment group. The results for Study NGF 200214 are shown in Table 2, similar results were found in study NGF0212.

Table 2 Primary Efficacy Analysis of Completely Staining Free Eyes at Week 8[6]

	rhNGF 20 mcg/mL N=23 n (%)	**Vehicle N=24 n (%)**	**Total N=48 n (%)**
Week 8			
Completely Staining Free	15 (65.2%)	4 (16.7%)	19 (40.4%)
Not Completely Staining Free	8 (34.8%)	20 (83.3%)	28 (59.6%)
Treatment Comparison [a] (rhNGF vs. Vehicle Control)			
Difference in % Complete Healing	48.6%		
95% CI [b]	(24.0, 73.1)		
p-value [c]	<0.001		

5 Risk Assessment & Safe-Use Conditions

The applicant acknowledges the small number of clinical trial subjects based on the rarity of the condition. Therefore, they included in the safety report all patients exposed to the product, even when used for other ocular indications. The primary safety pool included 177 stage 2 or 3 patients with NK

exposed to rhNGF 20 µg/ml. Eye disorders were the most common adverse events in all studies. During the controlled period where vehicle exposed patients provide a control population for comparison, eye related adverse events were experienced by 30/76 (39.5%) of vehicle treated subjects and 31/75 (41.3%) of rhNGF treated subjects. The eye disorder adverse event with a preponderance in the treated population was eye pain, which affected 12/75 (16%) of rhNGF treated subjects and 6/76 (7.9%) vehicle treated patients.[7] Based on higher occurrence in the rhNGF treated population, the non-severe treatment emergent adverse events of cataracts corneal deposits, corneal graft rejection, eye inflammation, eye pain, lacrimation increased, ocular hyperemia, and increased intraocular pressure, should be included in the adverse event labeling, per the clinical reviewer.[6]

5.1 DEATHS

In the primary safety pool, there were 8 deaths in patients treated with rhNGF and 1 in the vehicle treated group summarized below. The deaths were identified by an independent committee, contracted by Dompe, as not related to rhNGF.[1]

Table 3 Summary of Deaths in Pivotal Trial Subjects

		Controlled treatment period	**Follow-up period**
NGF0212	rhNGF 10 µg/mL (N=52)	1 (progression of squamous cell carcinoma)	1 (cardiac failure) 1 (myocardial infarction) 1 (arrhythmia and dyspnea) 1 (aortic dissection, aortic rupture, and hemorrhagic shock)
	rhNGF 20 µg/mL (N=52)	1 (lung cancer progression)	1 (respiratory failure)
	Vehicle (N=52)		1 (respiratory failure)
NGF0214	rhNGF 20 µg/mL (N=23)		1 (unknown cause)
	Vehicle (N=24)		

5.2 SERIOUS ADVERSE EVENTS

In the primary safety pool, eye disorder related serious treatment emergent adverse events occurred in 4/76 (5.2%) vehicle treated patients and 3/75 (4%) rhNGF treated patients. In the primary safety pool there was a single serious treatment emergent adverse event which occurred in the uncontrolled treatment period of reduced visual acuity.[7] No serious adverse events were identified by the

investigators as related to the study drug in either the primary or the secondary safety pool. The clinical reviewer assessed that serious adverse events reported for both studies were consistent with the underlying condition and patient population.

5.3 STERILITY

Sterile disinfectant wipes were used to clean the vials during clinical trials. The Agency has determined that sterile disinfecting wipes need to be co-packaged with the drug to reduce the risk of infection. The clinical reviewer stated that it is expected that all components required for self-administration (e.g., multi-dose vials, adapters, sterile wipes, pipettes) be included in the Oxervate box at the time it is dispensed) and be described in the labeling in sections 2.3 and 16.[6]

6 Expected Postmarket Use

Patients with neurotrophic keratitis are likely to be cared for by ophthalmologists, based on the rarity of the disease, and the significance of potential vision loss. As optometrists in some states have prescribing privileges, it is possible that they will be prescribing the product, along with ophthalmologists. Therefore, it is likely this drug will be prescribed by specialists in the care of eye diseases who will have the expertise to consider the risks and benefits of the drug for their patients. It is anticipated that this drug will be dispensed by outpatient pharmacies.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Oxervate beyond routine pharmacovigilance and labeling.[7]

8 Discussion of Need for a REMS

The clinical reviewer concludes that the available data establishes both the efficacy and safety of Oxervate 20 µg/ml dosed 6 times daily for 8 weeks for the treatment of Stage 2 and Stage 3 neurotrophic keratitis.[6] Neurotrophic keratitis is a rare, vision threatening disorder of the eye, that currently lacks effective treatment options. Two randomized, vehicle controlled, double blinded, superiority studies demonstrated the superiority of Oxervate to vehicle. Treatment with 20 µg/ml of Oxervate resulted in 29-49% more subjects having complete healing of their diseased eyes than those who received only the vehicle composed eye drops. The risks associated with Oxervate are localized to the eye, of mild to moderate severity. The isolated nature of the disease to the eye and the likely prescribing population should be familiar with the risks and contraindications for Oxervate, which are similar to other eye treatments, further support the lack of necessity for any additional risk mitigation beyond labeling for Oxervate. The necessity of supplying sterile disinfectant wipes in the product

packaging was incorporated into the labeling to reduce the potential risk of infection when the vial is accessed, and additionally will be co-packaged with the product. Therefore, risk mitigation beyond labeling is not warranted at this time.

9 Conclusion & Recommendations

Based on the available data, the benefit-risk profile is favorable therefore, DTOP and DRISK agree a REMS is not necessary for Oxervate's use for the treatment of neurotrophic keratitis to ensure the benefits outweigh the risks. At the time of this review, the labeling review was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

1. Dompe. For BLA 761094 Reports of Efficacy and Safety Studies 5.3.5.3 Review of Fatal Serious Adverse Events reported in studies of rhNGF eye drops. (December 22, 2017).
2. Alberding D. DTOP for BLA 761094 Mid-Cycle Communication. (May 1, 2018).
3. Alberding D. DTOP DRAFT BLA 761094 Late Cycle Meeting Minutes (July 6, 2018).
4. Davis EA, Dohlman CH. Neurotrophic keratitis. *International ophthalmology clinics.* 2001;41(1):1-11.
5. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clinical ophthalmology (Auckland, NZ).* 2014;8:571-579.
6. Lloyd R. BLA 761094 Clinical Review Draft. 2018(May 22, 2018).
7. Dompe. Orig-1 For BLA 761094 Clinical Overview & Integrated Summary of Safety. (December 22, 2017).

10.2 Etiologies of Neurotrophic Keratitis

Infection

Herpes simplex, Herpes zoster, Leprosy

Fifth nerve palsy

Surgery (as for trigeminal neuralgia), Neoplasia (e.g., acoustic neuroma), Aneurysms,

Facial trauma, Congenital, Familial dysautonomia (Riley-Day syndrome), Goldenhar-Gorlin syndrome,

Mobius syndrome, Familial corneal hypesthesia,

Topical medications

Anesthetics, Timolol, Betaxolol, Sulfacetamide, Diclofenac sodium,

Corneal dystrophies

Lattice, Granular (rare)

Systemic disease

Diabetes mellitus, Vitamin A deficiency

Iatrogenic

Contact lens wear, Trauma to ciliary nerves by laser and surgery (primarily for retinal conditions), Corneal incisions

Toxic

Chemical burns, Carbon disulfide exposure, Hydrogen sulfide exposure

Miscellaneous

Increasing age, Dark eye color Adie's syndrome

Any condition causing chronic corneal epithelial injury or inflammation

Source: From EB Groos, Neurotrophic keratitis. In: JH Krachmer, MJ Mannis, EJ Holland, eds. Cornea: clinical diagnosis and management. St. Louis: Mosby, 1997:1340.

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