CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Memo

NDA Number	212520
Link to EDR	EDR Link
Applicant	RevitaLid, Inc.
Drug, Dosage Form and Strength	Oxymetazoline HCl ophthalmic solution, 0.1% (Each drop of ophthalmic solution contains 0.035 mg oxymetazoline hydrochloride, equivalent to 0.0308 mg of oxymetazoline free base.)
Submission Type	Standard; 505(b)(2)
Submission Date	09/16/2019
PUDFA Goal Date	07/16/2020
Proposed Indication	Treatment of acquired blepharoptosis (b) (4) in adults
Proposed Dosing Regimen	One drop in each eye once daily
Associated IND	116915
OCP Division	Division of Inflammation and Immune Pharmacology
OND Division	Division of Ophthalmology
OCP Review Team	Amit A. Somani, B. Pharm., Ph. D. Clinical Pharmacology Reviewer, DIIP Bhawana (Bavna) Saluja., Ph. D. Clinical Pharmacology Team Leader, DIIP
OCP Final Signatory	Bhawana (Bavna) Saluja., Ph. D.

Table of Contents

SUMMARY and REVIEW 3

1.1 Recommendations 7

SUMMARY and REVIEW

The Applicant, Revitalid, Inc., has submitted NDA 212520 for oxymetazoline HCl ophthalmic solution, 0.1% (RVL-1201) under the 505(b)(2) pathway seeking marketing approval for the proposed indication of "*treatment of acquired blepharoptosis* [redacted] *in adults*". The proposed dosing regimen is one drop of oxymetazoline hydrochloride (HCl) ophthalmic solution), 0.1% into each eye once daily. As per the Applicant, oxymetazoline is an imidazoline derivative with sympathomimetic activity and believed to be a mixed α1/α2-adrenoceptor agonist. It is commonly used as a vasoconstrictor in eye drops and nasal sprays. Oxymetazoline HCl at 0.025% concentration is the active ingredient in over-the-counter (OTC) eye drops indicated for the relief of redness of the eye due to minor eye irritations: Ocuclear Eye Drops was approved in 1986, and Visine L.R. was approved in 1989. At 0.05% concentration, oxymetazoline HCl is the active ingredient in nasal spray formulation indicated for the temporary relief of nasal congestion and available OTC from multiple manufacturers. The first oxymetazoline HCl nasal spray, Afrin, was available by prescription in 1966 and has been available OTC since 1975. On January 28, 2017, RHOFADE™ (oxymetazoline hydrochloride) cream, 1% was approved under NDA 208552 for treatment of persistent facial erythema associated with rosacea in adults. In support of this 505(b)(2) application, Osmotica Pharmaceutical Corp (RevitaLid, Inc.) intends to rely on the FDA's previous findings of safety for RHOFADE cream, 1%, (oxymetazoline hydrochloride, NDA 208552). Each gram of RHOFADE™ cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base. The dosing recommendation for RHOFADE™ is application of pea-sized amount once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips.

NDA 212520 relies on clinical data from five clinical studies: one Phase 1 study that characterized the relative bioavailability and pharmacokinetics (PK) of oxymetazoline from the proposed product (RVL-1201) compared to RHOFADE™, the listed drug, one proof-of-concept Phase 1/2a study, and three pivotal Phase 3 studies which demonstrate the safety and efficacy of RVL-1201. As per the Applicant, the to-be-marketed formulation of RVL-1201 was used in the relative bioavailability study and the three Phase 3 studies. The focus of the Clinical Pharmacology review of this NDA was to assess and compare the systemic PK exposure of oxymetazoline for oxymetazoline HCl ophthalmic solution (RVL-1201) and RHOFADE™ (oxymetazoline hydrochloride) cream, 1% based on the phase 1 study RVL-1201-PKP01.

Study RVL-1201-PKP01 is a single-dose, 2-treatment, 2-period, 2-sequence, bioavailability study in which 24 healthy volunteers (i.e., male and female volunteers aged 18 to 45 years) received two separate single-dose administrations of study drug.

Study RVL-1201-PKP01 Methods and Results: The following two treatments were administered in the study subjects:

- Treatment A (test): One drop of oxymetazoline HCl ophthalmic solution, 0.1% to each eye
- Treatment B (reference): 0.3 g RHOFADE™ (oxymetazoline HCl) cream 1% applied to the entire face by the study volunteer

The total dose administered to each subject who completed both study periods was 0.07 mg (i.e., 0.035 X 2) of oxymetazoline HCl from one drop of RVL-1201 in each eye and 3 mg of oxymetazoline HCl from 0.3 g RHOFADE™.

Subjects were randomly assigned to one of the 2 treatment sequences. Subjects received either Treatment A or Treatment B on the morning of the first treatment period. In Period 2, subjects received the next treatment in their assigned treatment sequence. The treatment periods were separated by a washout period of 7 days.

Serial blood samples were collected for PK analysis at pre-dose, and 10, 20, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, and 36 hours post-dose. Each subject was scheduled to have 17 blood samples collected per period for PK analysis through 36 hours post-dose. All subjects completed both study periods, and 23 subjects were evaluable for PK analysis. One subject was excluded from PK analysis because pre-dose concentrations of oxymetazoline were observed in both periods that were greater than 5% of their respective C_{max} values. The mean plasma oxymetazoline concentration versus time profile can be seen in **Figure 1**.

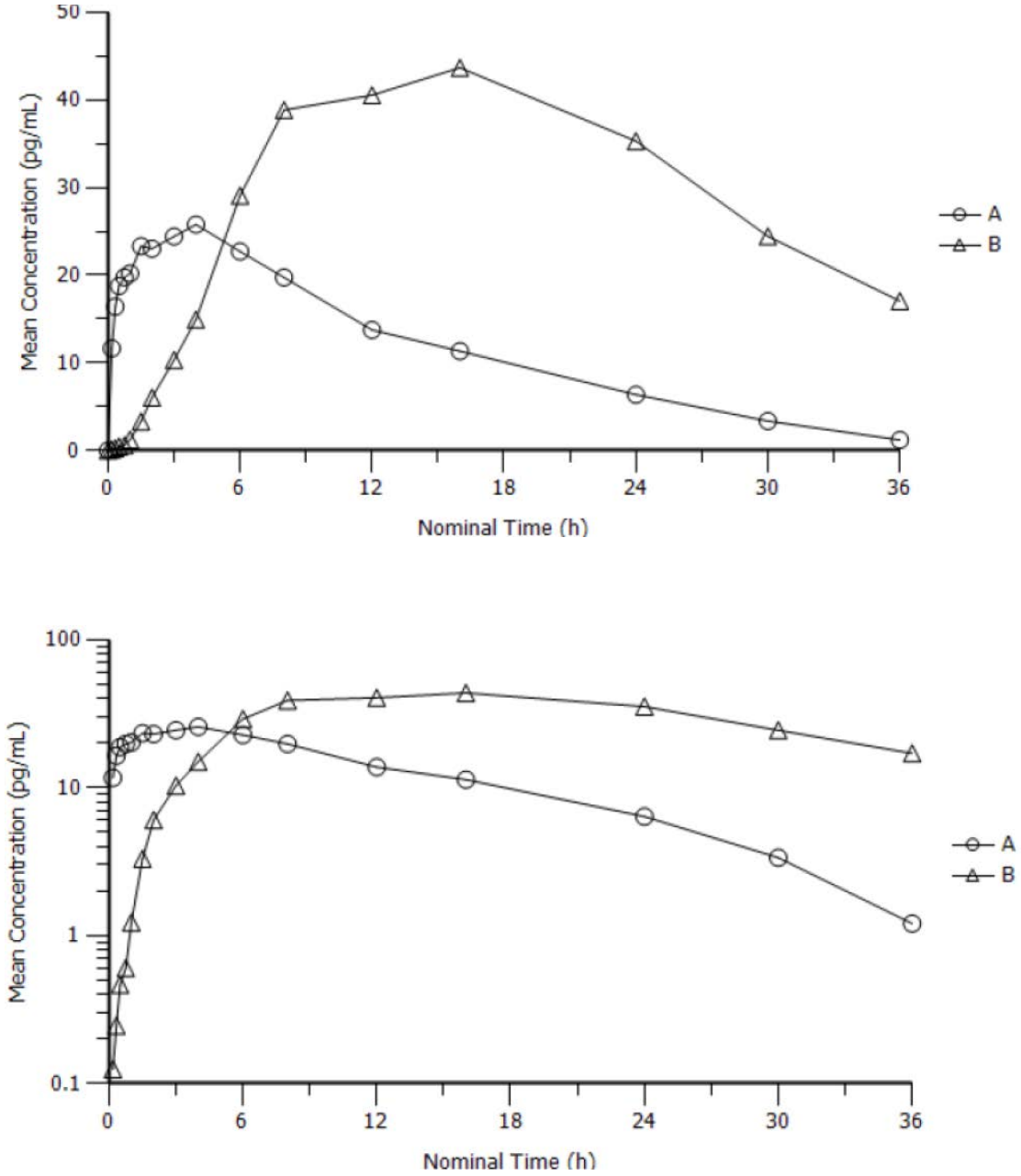

Figure 1. Mean Plasma Oxymetazoline Concentrations following Single-Dose Administration of RVL-1201 (Oxymetazoline HCl Ophthalmic Solution, 0.1%; Treatment A, Test) and 0.3 g RHOFADE™, 1% Cream (Treatment B, Reference) on Linear and Semi-Logarithmic Scales to Healthy Male and Female Volunteers, Study RVL-1201-PKP01 (N=23)

The PK parameters for oxymetazoline were calculated by non-compartmental methods and presented in **Table 1**.

Table 1. Summary of Oxymetazoline Pharmacokinetic Parameters for Oxymetazoline HCl Ophthalmic Solution (RVL-1201), 0.1% and RHOFADE™ (oxymetazoline HCl) Cream 1% in Healthy Adult Subjects

PK Parameter	Treatment A RVL-1201, Test		Treatment B RHOFADE™, Reference	
	N	Mean ± SD	N	Mean ± SD
T_{max} (hr)[a]	23	2 (0.5 - 12)	23	16 (8 - 24)
C_{max} (pg/mL)	23	30.5 ± 12.7	23	47.6 ± 28.3
AUC_{tlast} (hr*pg/mL)	23	400 ± 188	23	1080 ± 686
AUC_{inf} (hr*pg/mL)[b]	19	468 ± 214	9	950 ± 476
$t_{1/2}$ (hr)[c]	21	8.25 (5.6 - 13.9)	20	11.3 (8.1 - 17.6)

Treatment A: one drop of RVL-1201 (oxymetazoline HCl ophthalmic solution, 0.1%) to each eye (Test)
Treatment B: 0.3 g RHOFADE™ (oxymetazoline HCl, 1%) cream applied to the entire face (Reference)
[a] Median (range)
[b] AUC_{inf}: AUC_{inf} values with extrapolation > 20% were excluded from summary statistics.
[c] Harmonic mean (range)

Bioanalytical: Oxymetazoline was quantified in plasma using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. The lower and upper quantification limits for plasma oxymetazoline were 2.50 and 1500 pg/mL, respectively. Review summary of the information from the submitted bioanalytical validation and performance reports is provided in **Table 2.**

Table 2. Summary of the Bioanalytical Method

Validation Report	Validation report provided	☒Yes ☐No
	Validation report acceptable	☒Yes ☐No
Performance Report	Samples analyzed within the established stability period	☒Yes ☐No
	Quality control samples range acceptable	☒Yes ☐No
	Sample chromatograms provided	☒Yes ☐No
	Accuracy and precision of the calibration curve acceptable	☒Yes ☐No
	Accuracy and precision of the quality control samples acceptable	☒Yes ☐No
	Overall performance acceptable	☒Yes ☐No

Reviewer's Comment: *The systemic exposure (i.e., AUC and C_{max}) to oxymetazoline from the proposed clinical dose of RVL-1201 is lower compared to the exposures following administration of the approved dose of topically applied RHOFADE™ cream, which supports the establishment of a PK bridge between these two products from a clinical pharmacology perspective. The information submitted in support of the PI edits pertaining to clinical pharmacology sections appear mostly aligned with that currently stated in RHOFADE™ PI and reliance on RHOFADE™ PI for clinical pharmacology information (as discussed by the*

Applicant on page 2 of the reviewer's guide and elsewhere in NDA) in oxymetazoline HCl ophthalmic solution, 0.1% PI is acceptable to the review team.

1.1 Recommendations

The Clinical Pharmacology review team deems that the systemic PK exposure of oxymetazoline has been adequately characterized in this NDA for the oxymetazoline HCl ophthalmic solution, 0.1%. The Clinical Pharmacology relevant labeling edits are currently ongoing. This NDA is approvable from a clinical pharmacology perspective.

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/

AMIT A SOMANI
06/10/2020 12:58:43 PM

BHAWANA SALUJA
06/10/2020 01:01:46 PM