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APPLICATION NUMBER:

217064Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	217064
Supporting document/s:	1
Applicant's letter date:	11-28-2022
CDER stamp date:	11-28-2022
Product:	Phentolamine Ophthalmic Solution, 0.75%
Indication:	Treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof
Applicant:	Ocuphire Pharma, Inc
Review Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM) supporting the Division of Ophthalmology (DO)
Reviewer:	María I Rivera, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD (acting for Lori E. Kotch, PhD)
Division Director:	Mukesh Summan, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Ocuphire is submitting this NDA for Phentolamine Ophthalmic Solution 0.75% drug product pursuant to section 505(b)(2) of the Food, Drug, and Cosmetic (FD&C) Act. Phentolamine Ophthalmic Solution 0.75% is indicated for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof. The intended population include both adults and children (≥3 years of age). The maximal recommended dose intended for marketing is 2 drops in adults and 1 drop in children.

Ocuphire intends to rely on the Agency's previous findings of nonclinical systemic safety, clinical pharmacology, and systemic clinical safety for the approved listed drugs (LDs), Regitine® (NDA 008278) and OraVerse® (NDA 022159). To support the ophthalmic route of administration, indication, and formulation, the Applicant conducted original ocular toxicity studies. The Applicant is also relying on information available in the published literature to support phentolamine pharmacological activity, metabolism, and some toxicology elements.

To enable reliance on the proposed LDs, the Applicant has established a scientific bridge through demonstration of lower systemic phentolamine exposure in clinical trials conducted with Phentolamine Ophthalmic Solution 0.75% compared to data in the published literature for oral submucosal OraVerse® at the highest approved dose of 0.8 mg.

1.2 Brief Discussion of Nonclinical Findings

Based on the intended dosing regimen of a total of 1 to 2 drops, only the rabbit 5-day non-GLP and 28-day GLP studies were reviewed to support this NDA. The 6-month rabbit ocular toxicity study was not reviewed. The drug product concentration intended for marketing is 0.75% based on phentolamine, equivalent to 1% based on the mesylate salt. The concentrations below refer to the mesylate salt.

In the 5-day ocular tolerability study, no adverse findings were observed after treatment with phentolamine mesylate up to 1.5% BID for 4 days or 1.5% QID for 1 day (NOEL). Slight conjunctival redness, swelling and discharge were observed at 2% QID administered for 3 days (NOAEL). Severe ocular irritation was observed at 5% QID. Animals displayed head shaking, partial palpebral closure, rubbing/pawing of the treated eyes, slight to moderate discharge, redness, and swelling, iritis, sloughing of the nictating membrane, and slight dulling of the normal luster of the cornea.

In the 28-day ocular toxicity study, isolated occurrences of conjunctival redness and discharge, and corneal opacity (involving < 25% of the cornea) were observed at

≤1% QID (NOAEL). Conjunctivitis (redness, swelling and discharge), ocular surface hyperemia (slight), and corneal opacities (involving <25 to 75% of the cornea) were observed mainly at 2.0% QID. No adverse systemic effects were observed.

As noted by the Applicant, the conjunctival redness could be associated with the pharmacological activity of phentolamine as an alpha-adrenergic antagonist (vasodilation).

The 2.0% QID NOAEL from the 5-day ocular tolerability study provides ocular exposure margins of 6.7X (adults) and 13X (children). The 2.0% NOAEL from the 28-day ocular toxicity study provides ocular exposure margins of 2.7X (adults) and 5.3X (children). Based on the intended total dose of 1 or 2 drops per eye and longer treatment duration in these nonclinical studies, the exposure margins are expected to be higher.

Systemic safety is supported by the lower systemic phentolamine exposure observed in the clinic after treatment with Phentolamine Ophthalmic Solution 0.75% compared to data in the published literature for oral submucosal OraVerse® at the highest approved dose of 0.8 mg. In addition, the systemic exposure in the clinical trials (C_{max} ≤ 0.71 ng/mL and AUC ≤ 1.31 ng•hr/mL) was lower than that observed in the 28-day ocular toxicity study (C_{max} ≤ 46.8 ng/mL and AUC≤ 67 ng•hr/mL), at which no adverse systemic effects were observed.

The nonclinical data support the ocular and systemic safety of Phentolamine Ophthalmic Solution 0.75% (or 1% as the mesylate salt) at the intended dosing regimen for marketing.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Applicant's Proposed Text	Reviewer's Recommendations
INDICATIONS AND USAGE Phentolamine Ophthalmic Solution 0.75% is indicated for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g.,	INDICATIONS AND USAGE Phentolamine Ophthalmic Solution 0.75%, an alpha-adrenergic blocker, is indicated for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine)…

tropicamide) agents, or a combination thereof. (1)	
8.1 Pregnancy Risk Summary There are no available data with Phentolamine Ophthalmic Solution 0.75% administration in pregnant women to inform a drug-associated risk. In animal toxicology studies, when phentolamine was administered orally to pregnant mice and rats during the period of organogenesis skeletal immaturity and decreased growth was observed in the offspring at doses at least 24-times the recommended clinical dose. Additionally, a lower rate of implantation was seen in pregnant rats treated with phentolamine administered at least 60-times the recommended clinical dose. No malformations or embryofetal deaths were observed in the offspring of pregnant mice, rats, and rabbits administered phentolamine during the period of organogenesis at doses of at least 24-, 60-, and 20-times, respectively, the recommended clinical dose [*see Data*]. Phentolamine Ophthalmic Solution 0.75% should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. Data Animal Data Oral administration of phentolamine to pregnant rats and mice at doses at least 24-times the recommended clinical dose (based on a body weight per surface area (mg/m^2) comparison with a 60-kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calcanei and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 60-times the recommended clinical dose (based on a mg/m^2 comparison with a 60-kg human), a slightly lower rate of implantation was found in rats. Phentolamine did not affect	**8.1 Pregnancy** No edits are recommended.

embryonic or fetal development in rabbits at oral doses at least 20-times the recommended dose (based on a mg/m^2 comparison with a 60-kg human). No malformations or embryofetal deaths were observed in the rat, mouse or rabbit studies.	
8.2 Lactation Risk Summary There is no information regarding the presence of phentolamine in human milk, the effects on the breastfed infants, or the effects on milk production during lactation to inform risk of Phentolamine Ophthalmic Solution 0.75% to an infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Phentolamine Ophthalmic Solution 0.75% and any potential adverse effects on the breastfed child from Phentolamine Ophthalmic Solution 0.75%.	**8.2 Lactation** No edits are recommended.
12.1 Mechanism of Action Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic antagonist. Dilation of the pupil is controlled by the radial iris dilator muscles surrounding the pupil; these muscles are activated by the alpha-1 adrenergic receptors. Phentolamine reversibly binds to these receptors on the iris dilator muscle, thereby reducing pupil diameter. Phentolamine directly antagonizes the mydriatic effect of an α-1 adrenergic antagonist, and indirectly reverses mydriasis induced by muscarinic antagonist effects on the iris sphincter muscle.	**12.1 Mechanism of Action** No edits are recommended.

13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** Carcinogenicity studies with Phentolamine Ophthalmic Solution 0.75% have not been conducted. **Mutagenesis** Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phentolamine without metabolic activation, and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in-vivo mouse micronucleus assays. **Impairment of Fertility** The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine for nine weeks (four weeks prior to mating, 3 weeks during the mating period and 2 weeks after mating) were mated with untreated females. At doses up to (b) (4) times human therapeutic exposure levels at the Cmax, no adverse effects on male fertility parameters or on reproductive parameters in the untreated females mated with the treated males were observed.	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** No edits are recommended to Carcinogenesis and Mutagenesis sections. **Impairment of Fertility** The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine for nine weeks (four weeks prior to mating, 3 weeks during the mating period and 2 weeks after mating) were mated with untreated females. At doses up to (b) (4) 648-times human therapeutic exposure levels at the Cmax, no adverse effects on male fertility parameters or on reproductive parameters in the untreated females mated with the treated males were observed.

Exposure Margins Calculations:

Pregnancy (8.1)

Exposure margins were not updated by the Applicant; they are the same as found in the approved OraVerse® label.

OraVerse® used data from Regitine®, Regitine® label did not specify the doses evaluated in the reproductive toxicity studies. Regitine® was approved on 1952, and no review appears in DARRTS or Drug@FDA.

Given the doses are not specified in the approved OraVerse® or Regitine® labels, the exposure margins could not be updated for the current recommended dose. Based on the mesylated form of phentolamine, the OraVerse® dose is 1.33X higher than the maximal recommended dose for Phentolamine Ophthalmic Solution (1%). Therefore, the language used in the OraVerse® label of "at least X-exposure margin" is applicable to Phentolamine Ophthalmic Solution. As such, no updates to the exposure margins are necessary.

- Phentolamine Ophthalmic Solution maximal recommended ophthalmic dose = 2 drops/eye (total of 4 drops, 30 µL drop volume) = 1.2 mg/day (mesylate form) or 0.9 mg/day (phentolamine)

- OraVerse® maximal recommended dose = 2 cartridges (0.8 mg each) = 1.6 mg/day (mesylate form)

Impairment of Fertility (13.1):

- The exposure margin was updated from 143X in the OraVerse® label to (b) (4)X in the proposed label.
- The OraVerse® nonclinical review is available on Drugs@FDA. Per information in OraVerse® nonclinical review (page 47), male rats were treated with 0, 10, 75 and 150 mg/kg/day phentolamine mesylate orally by gavage in distilled water for 9 weeks; 4 weeks prior to mating and 3 weeks during the mating period, and 2 weeks after mating prior to sacrifice. The NOEL for reproductive toxicity and fertility was the high dose, 150 mg/kg/day. The C_{max} was 389 ng/mL on Day 1 and 707 ng/mL on Day 13.
- On Section 12.3 Pharmacokinetics of the Phentolamine Ophthalmic Solution 0.75% proposed label, phentolamine C_{max} is (b) (4) ng/mL (b) (4) drops). Therefore, this reviewer calculated the exposure margins as 389 (b) (4) = 648X and 707/(b) (4) = 1178X.
- It appears the Applicant used a human C_{max} of (b) (4) ng/mL (found on page 11 and 12 of Module 2.7.2 Summary of Clinical Pharmacology) to calculate the exposure margin of (b) (4)X ((b) (4). This reviewer believes it is more appropriate to use the human C_{max} value reported on Section 12.3 Pharmacokinetics of the proposed label.

2 Drug Information

2.1 Drug

CAS Registry Number: 65-28-1

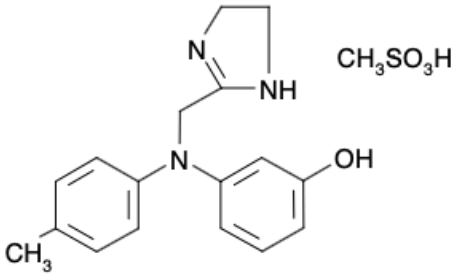
Generic Name: Phentolamine Mesylate

Code Name: (b) (4)

Chemical Name: Phenol,3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl] (4-methyl phenyl)amino]-monomethanesulfonate (salt)

Molecular Formula/Molecular Weight: $C_{17}H_{19}N_3O * CH_4O_3S$

Structure:



Pharmacologic Class: alpha adrenergic blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 070499
- NDA 008278 (Regitine®, Ciba, now Novartis; approved January 1952)
- NDA 022159 (OraVerse®, Novalar, approved May 2008)
- DMFs (b) (4)

2.3 Drug Formulation

The Phentolamine Ophthalmic Solution Drug Product (DP) is a non-preserved aqueous solution contained within a 0.5 mL single-dose low-density polyethylene (LDPE) blow-fill-seal (BFS) vial intended for topical administration directly to the eye. The composition of the drug product is shown in Table 1.

Table 1: Drug Product Composition

Ingredient and Quality Reference	Purpose	Composition (% w/v)	Amount per mL (mg/mL)	IDD levels[1]	
				Maximum Potency per unit dose (for Ophthalmic solution) (% (w/v))	Maximum Daily Exposure (MDE)
		0.75% Phentolamine	0.75% Phentolamine		
Phentolamine Mesylate, cUSP	Drug substance	1.0	10.00	Not applicable	Not applicable
Mannitol, cUSP	(b) (4)				No details given
Sodium Acetate Trihydrate, cUSP					No details given
(b) (4) Sodium Hydroxide, cNF	pH adjustment	Adjust to pH 4.5– (b) (4)	Adjust to pH 4.5– (b) (4)		No details given
(b) (4) Hydrochloric Acid, cNF	pH adjustment	Adjust to pH 4.5– (b) (4)	Adjust to pH 4.5– (b) (4)		No details given
Water for Injection, cUSP	Dilution medium	q.s. to 1.00 g	q.s. to 1.00 mL	Not applicable	Not applicable
Nitrogen, cUSP	(b) (4)	As required	As required	Not applicable	Not applicable

cNF = current National Formulary; cUSP = current United States Pharmacopoeia; q.s. = as much as suffices
** Adjustment pH

Source: Sponsor's Table 1, EDR Module 2.3.P Drug Product

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

See Section 10. Special Toxicology Studies of this review for nonclinical data to support the proposed specification of NMT (b) (4) % for (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

- Adults and children aged 12 years and older: Instill 1 to 2 drops in each dilated eye following the completion of the ophthalmic examination or procedure to reverse mydriasis.
- In children aged 3 to 11 years: Instill 1 drop in each dilated eye following the completion of the ophthalmic examination or procedure to reverse mydriasis.

2.7 Regulatory Background

- Pre-IND submitted 3-16-2005; Sponsor meeting held 4-29-2005.
    - The Division agreed with the use of only one species for ocular toxicity evaluation

- Initial IND submitted 7-30-2011 (nonclinical review filed in DARRTS on 8-26-2011, Lansita)

- Type C meeting briefing package submitted on 10-8-2012 (nonclinical review filed in DARRTS on 10-31-2012, Rivera; Sponsor meeting held on 11-6-2012)
    - Advice was given on the study design of a 6-month ocular toxicity study to support chronic dosing in humans and inclusion of histopathology evaluation for a 3-month interim sacrifice and timing of study report submission relative to Phase 3 study progression.

- End-of-phase 2 meeting briefing package submitted on 3-17-2020 (nonclinical review filed in DARRTS on 4-29-2020, Rivera; Sponsor meeting held on 5-11-2020)
    - The Sponsor sought feedback for the adequacy of the development plan for several indications including “reversal of pharmacologically induced mydriasis”.
    - Further advice was given for the design of the 6-month ocular toxicity study.
    - Recommendations were given for a nonclinical combination study if a fixed-dose combination with approved ocular hypotensive agents is pursued.

- Pre-NDA Type B meeting briefing package submitted 5-24-2022 (nonclinical review filed in DARRTS on 6-16-2022, Rivera; Sponsor meeting held 6-24-2022)
    - The Division agreed that the nonclinical development program was sufficient to support NDA submission for the indication of “reversal of pharmacologically induced mydriasis”.
    - The Division agreed with the proposed plan to establish a scientific bridge through the demonstration of lower phentolamine exposure between the proposed topical ophthalmic product and the approved listed drugs.

3 Studies Submitted

3.1 Studies Reviewed

- A 5-Day Study of Phentolamine Mesylate by Ocular Administration in Rabbits (Study No. 20011929)

- Studies previously reviewed under IND 070499 30-day safety review:

    - A 28-day GLP Study of Phentolamine Mesylate by Topical Ocular Administration in Dutch-Belted Rabbits (Study No. 20011189)
    - TK Report of the 28-day ocular toxicity rabbit study (Study No. MC11R-0023)

- Studies briefly reviewed under IND 070499 30-day safety review since the proposed trial was supported by the 28-day rabbit study for which a full review was conducted.
    - Ocular toxicity dose-ranging study in New Zealand White rabbits (Study No. NP101105)

3.2 Studies Not Reviewed

- A 6-Month Topical Ocular Toxicity and Toxicokinetic Study of Phentolamine Ophthalmic Solution in Dutch-Belted Rabbits with an 8-Week Recovery (Study No. 0460LO39.003)
- TK Report of the 6-Month Ocular Toxicity Study (Study No. MC21R-0015)
    - Both study reports were not reviewed because the intended dosing regimen is only 1 or 2 drops on a single day and there is a 28-day ocular toxicity study
- Module 4.2.2.1 Analytical Methods and Validation Reports

3.3 Previous Reviews Referenced

- Initial IND 70499 review (Lansita, filed in DARRTS on 8-26-2011)
- NDA 022159 (OraVerse®, approved May 2008)

4 Pharmacology

Phentolamine mesylate is a non-selective alpha-1 and alpha-2 adrenergic antagonist (blocker). Phentolamine is known to inhibit contraction of the iris dilator muscle, resulting in a smaller pupil. The iris dilator muscles contain predominantly α-1 adrenergic receptors that can be inhibited by α-1 antagonists. Pupil size is under the control of 2 opposing sets of muscles – the iris sphincter muscles controlled by the cholinergic nervous system and the iris dilator muscles controlled by the adrenergic nervous system. Therefore, it is possible to inhibit dilation (mydriasis) of the pupil with

an α-1 adrenergic antagonist that can either directly antagonize the α-1 agonist or indirectly antagonize the pupil dilation effect of muscarinic antagonists.

Mild, transient redness is also observed with topical ocular administration of phentolamine due to its on-target effect of vasodilation of conjunctival blood vessels.

Phentolamine mesylate can lower intraocular pressure (IOP), likely related to decreasing episcleral venous pressure or increasing uveoscleral outflow. No significant effects on IOP were observed in the 28-day ocular toxicity study in rabbits.

As the primary pharmacodynamics of phentolamine mesylate is well established, including pharmacological activity in the eye, no additional primary pharmacology studies were conducted by the Applicant.

4.3 Safety Pharmacology

No formal studies were conducted.

The following safety pharmacology information (in italics) upon which the Applicant intends to rely is reported in the approved product labeling for OraVerse®:

"Tachycardia and cardiac arrhythmias may occur with the use of phentolamine or other alpha-adrenergic blocking agents."

The Applicant considers this class risk to be minimal due to the low systemic exposure of phentolamine mesylate following topical ocular administration. The Applicant indicated that no effects on mean systolic blood pressure, diastolic blood pressure, or heart rate compared to placebo were observed in their clinical trials. This reviewer agrees there is minimal clinical concern for cardiovascular effects at the intended dosing regimen of a total of 1 to 2 drops per eye.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Following topical ocular administration to rabbits (28-day ocular toxicity rabbit study, Study No. 20011189 below), phentolamine was readily absorbed into the systemic circulation with mean T_{max} generally occurring within 0.25 hour on Day 1 and Day 28 following the last dose administration. The $t_{1/2}$ of 0.5%-2.0% phentolamine mesylate ranged from approximately 1 to 1.4 hours. Exposure (plasma concentrations and AUC) increased between Day 1 and Day 28 indicating some accumulation.

Overall (both days and gender combined), the systemic exposure in the 28-day ocular toxicity study ranged from 3.30 to 46.8 ng/mL (C_{max}) and 5.4 to 67.2 ng•hr/mL (AUC) (Table 2).

Table 2: Mean Phentolamine Toxicokinetic Parameters – 28-Day Rabbit Ocular Toxicity Study

Day	% Phentolamine Mesylate	Male			Female		
	Dose, µg/day	1600	3200	6400	1600	3200	6400
	Dosing Solution	0.5	1	2	0.5	1	2
1	Cmax, pg/mL	3,300	4,780	19,300	7,220	8,550	46,800
	Tmax, h[a, b]	6.25	6.25	6.25	6.25	6.25	6.25
	$T_{1/2}$, h[c]	0.897	1.05	1.16	0.972	1.02	1.02
	AUC(0-T), pg·h/mL	5,400	9,910	35,200	9,310	14,300	67,200
	Cmax Ratio (F/M)	2.19	1.79	2.42	-		
	AUC(0- T) Ratio (F/M)	1.72	1.44	1.91	-		
28	Cmax, pg/mL	3,980	3,950	17,000	10,300	13,100	24,200
	Tmax, h[a]	6.25	6.25	6.25	6.25	6.25	6.25
	$T_{1/2}$, h[b]	1.09	1.36	1.21	0.833	1.08	1.09
	AUC(0-T), pg·h/mL	7,600	8,680	26,800	13,100	17,800	49,300
	Cmax Ratio (F/M)	2.59	3.32	1.42	-		
	AUC(0- T) Ratio (F/M)	1.72	2.05	1.84	-		
	Cmax Ratio (Day 28/Day 1)	1.21	0.826	0.881	1.43	1.53	0.517
	AUC(0-T) Ratio (Day 28/Day 1)	1.41	0.876	0.761	1.41	1.24	0.734

[a] Expressed as median
[b] Median Tmax equals 0.250 hour relative to fourth dose time
[c] Expressed as harmonic mean

Source: Study Report, Toxicokinetic Report (Appendix 18), Table 7

Per the Applicant, there was very low systemic exposure of phentolamine after topical ocular administration, with a mean C_{max} of 0.53 ng/mL and $AUC_{(0-3)}$ of 0.98 ng•hr/mL after a single, bilateral topical ocular dose (based on PK data from OPI-NYXRM-302 (MIRA-3) of 3 drops of Phentolamine Ophthalmic Solution (total 0.9 mg phentolamine mesylate) and the estimated exposure (assuming linearity) with the maximum dose of 4 drops (1.2 mg phentolamine mesylate) with C_{max} of 0.71 ng/mL and $AUC_{(0-3)}$ of 1.31 ng•hr/mL.

Therefore, the systemic exposure in the clinical trials was lower than that observed in the 28-day ocular toxicity study. No adverse systemic effects were observed in this nonclinical study.

Reviewer's comments: *The Applicant is using a clinical C_{max} of* (b) (4) *ng/mL in Section 12.3 Pharmacokinetics of the proposed label.*

6 General Toxicology

6.2 Repeat-Dose Toxicity

Rabbit 5- or 3-Days Ocular Tolerability Study

A 5-Day Study of Phentolamine Mesylate by Ocular Administration in Rabbits (Study # 20011929; non-GLP) – Male Dutch-belted rabbits received a drop of phentolamine mesylate BID for 4 days and QID for 1 day at concentrations of 0.5%, 1.0%, and 1.5% (Table 3). Animals were kept on a dosing-free period during Days 6 to 9. Dosing was resumed on Days 10 to 12 at phentolamine mesylate concentrations of 0% (8% mannitol), 2.0%, or 5.0% QID (Table 4). The test material was instilled into the conjunctival sac of the right eye of each animal. The left eye was a non-treated control.

Table 3: Study Design – Days 1 to 5 - 5-Day Ocular Tolerability Study

Group No.	No. of Main Animals Males	Dose Material	Dose Level (mg/kg/day)	Dose Volume (µL)	Dose Concentration (mg/mL)
1	3	Phentolamine mesylate	0.5% BID[a]	(b) (4)	5
2	3	Phentolamine mesylate	1.0% BID[a]		10
3	3	Phentolamine mesylate	1.5% BID[a]		15

BID = twice daily dose administration.
[a] On Day 5, animals were dosed 4 times.

Table 4: Study Design – Days 10 to 12 - 5-Day Ocular Tolerability Study

Group No.	No. of Main Animals Males	Dose Material	Dose Level (mg/kg/day)	Dose Volume (µL)	Dose Concentration (mg/mL)
1	3	(b) (4) Mannitol	0% QID	(b) (4)	0
2	3	Phentolamine mesylate	2.0% QID		20
3	3	Phentolamine mesylate	5.0% QID		50

QID = 4 times a day dose administration.

The following parameters and endpoints were evaluated: clinical signs, ocular observations, pupil diameter measurements, and ocular surface hyperemia scoring.

Key findings:

- Ocular administration of phentolamine mesylate ([(b) (4)]µL/dose) BID for 4 days and QID for 1 day was well tolerated in rabbits at concentrations of 0.5%, 1.0%, and 1.5%.
- Ocular administration of phentolamine mesylate QID for 3 days was well tolerated in rabbits at a concentration of 2.0%, while administration at a concentration of 5.0% was considered overtly irritating to the eye and would not be suitable for longer term studies.
    - Following administration of 5.0% phentolamine mesylate QID on Days 10-12, the animals displayed head shaking, partial palpebral closure, and rubbing/pawing of the treated eyes.
    - Ocular findings at 2.0% phentolamine mesylate on Days 10-12 included slight conjunctival discharge, redness, and swelling.
    - Administration of 5.0% phentolamine mesylate resulted in slight to moderate conjunctival discharge, redness, and swelling; iritis; sloughing of the nictating membrane; and slight dulling of the normal luster of the cornea.
    - Administration of 5.0% phentolamine mesylate on Days 10-12 produced a modest reduction in pupil diameter in the treated (right) eye.
    - Slight vessel injection (hyperemia) (score of +0.5) was noted at 2.0% phentolamine mesylate, while slight to moderate vessel injection (scores of +0.5 to +2) was noted at 5.0% phentolamine mesylate.
    - Slight vessel injection was noted in a single untreated (left) eye on Day 10.
- Ocular administration of 8% mannitol 4 QID for 3 days was well tolerated in rabbits.

Rabbit 28-Day GLP Ocular Toxicity Study

An audited draft report was submitted with the initial IND and reviewed by Dr Lansita (filed in DARRTS on 8-26-2011). The final report was submitted to the IND under SDN-27 (3-25-2020). There were no significant changes that will impact the conclusions initially reached. Dr Lansita's review for this study report is copied below. Additional comments by this reviewer are shown in italics.

Study title: A 28-day GLP Study of Phentolamine Mesylate by Topical Ocular Administration in Dutch-Belted Rabbits

Study no.:	20011189
Study report location:	EDR Module 4.2.3
Conducting laboratory and location:	[(b) (4)]
Date of study initiation:	March 7, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phentolamine Mesylate, M90768, 98.5%

Key Study Findings

- The main study findings include conjunctivitis (redness, swelling and discharge) and corneal opacities observed mainly in the 2.0% dose group.
- No intraocular changes were observed.
- The NOAEL was 1.0% QID.

Methods

Doses:	0, 0.5% (5 mg/mL), 1.0% (10 mg/ml), 2.0% (20 mg/ml) ***Note:*** *These are expressed as the mesylate form and are equivalent to 0, 0.375, 0.75, and 1.5% phentolamine, respectively.*
Frequency of dosing:	QID, four times per day to both right and left eyes, 2 hours +/- 10 min between doses from Days 1 to 28
Route of administration:	Ocular topical
Dose volume:	40 uL
Formulation/Vehicle:	(b) (4) Mannitol, (b) (4) Sodium Acetate (trihydrate) in purified water (pH (b) (4)
Species/Strain:	Rabbit/Dutch belted
Number/Sex/Group:	5/sex/group
Age:	27 weeks
Weight:	2.3-2.6 kg males, 2.2-2.6 kg females
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	*None with an impact on study validity of data interpretation*

Observations and Results

Mortality (2X/day)

None test article related

Clinical Signs (Prestudy and once daily on Days 1-29)

Ocular discharge was seen in several animals, mainly in the 2.0% dose group. See further detail on the ocular findings in the Ocular Observations and Ophthalmoscopy section below. No other general clinical signs were observed.

Body Weights (Prestudy and once daily Days 1-29)

No test article-related effects

Feed Consumption (Daily)

No test article-related effects

Ophthalmoscopy (Ocular surface hyperemia scoring prestudy, twice daily, Days 1-22 and once on Day 29; intraocular pressure prestudy and weekly; Draize twice daily 1-22 and Day 29; Slit-lamp biomicroscopy [with fluorescein staining] using Hackett- McDonald scoring and indirect ophthalmoscopy, weekly and prior to termination)

Macroscopic observations included conjunctivitis (redness, swelling, and discharge) and corneal opacities that were seen mainly in animals treated with 2.0% phentolamine mesylate. Discharge was of marked severity in the 2.0% treated animals *(severity ranged from 1 to 2 indicating above normal to abundant discharge).* Macroscopic changes in lower dose animals were also seen and included isolated cases of conjunctival discharge, conjunctival redness, and corneal opacities.

Two types of corneal opacities were seen (Tables 5 and 6). One type of corneal opacity was observed in controls and across dose groups; these opacities were characterized as focal to multifocal, scattered and diffuse in density over areas of less than one quarter of the eye. The second type of opacity was seen mainly in animals treated at 2.0% phentolamine mesylate; these opacities were characterized as patchy, mild to moderate opacities, over larger areas 26-75% in the nasal and ventro-nasal quadrants. The Applicant notes that the focal/multifocal opacities seen in controls and animals across dose groups were likely due to irritation. However, there does appear to be a greater number of observations described as “opacity/area-1” and “opacity/density-1” in treated females compared with control females (Table 5). Therefore, a treatment related effect cannot be ruled out in these animals. The opacities primarily seen in animals treated with 2.0% phentolamine mesylate appear to be treatment related. Macroscopic irritation and hyperemia were also seen at 2.0%.

Table 5: Macroscopic Ocular Observations in Male Rabbits: Total Number of Observations/Number of Males Affected

Dose Level (%)	0		0.5		1		2	
Diagnoses/ Eye	Left	Right	Left	Right	Left	Right	Left	Right
Discharge	0/0	0/0	1/1	1/1	0/0	0/0	14/5	25/5
Swelling	0/0	0/0	0/0	0/0	0/0	0/0	7/3	12/3
Redness	0/0	0/0	0/0	0/0	0/0	0/0	24/4	29/4
Opacity/Area-1	14/1	26/3	17/1	5/1	2/1	17/1	15/3	28/3
Opacity/Density-1	14/1	26/3	17/1	5/1	2/1	17/1	15/3	28/3
Opacity/Area-2	0/0	0/0	0/0	0/0	0/0	0/0	3/1	1/1
Opacity/Density-2	0/0	0/0	0/0	0/0	0/0	0/0	3/1	2/1

Table 6: Macroscopic Ocular Observations in Females Rabbits: Total Number of Observations/Number of Females Affected

Dose Level	0		0.5		1		2	
Diagnoses/ Eye	Left	Right	Left	Right	Left	Right	Left	Right
Discharge	0/0	0/0	0/0	0/0	0/0	0/0	28/5	25/5
Swelling	0/0	0/0	0/0	0/0	0/0	0/0	21/5	15/5
Redness	0/0	0/0	0/0	0/0	0/0	1/1	40/5	32/5
Opacity/Area-1	0/0	2/1	1/1	1/1	0/0	0/0	8/3	16/3
Opacity/Density-1	0/0	2/1	1/1	1/1	0/0	0/0	12/3	18/4
Discharge-2	0/0	0/0	0/0	0/0	0/0	0/0	7/3	2/2
Opacity/Area-2	0/0	0/0	0/0	0/0	0/0	0/0	3/1	0/0
Slight Dulling of Normal luster of cornea	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Opacity/Area-3	0/0	0/0	0/0	0/0	0/0	0/0	1/1	2/2

Ocular surface hyperemia was seen mainly in males and females at 2.0% (Table 7). In males, vessel injection above normal was also observed in control and 1.0% animals. However, the findings at 2.0% appear to be treatment related since the total number of observations and the number of males affected was higher at 2.0%.

Table 7: Ocular Surface Hyperemia in Male and Female Rabbits: Total Number of Observations/Number of Animals Affected

Dose Level	0		0.5		1.0		2.0	
Diagnoses/ Eye	Left	Right	Left	Right	Left	Right	Left	Right
Males - Vessel injection slightly above normal	2/1	1/1	0/0	0/0	3/1	2/1	5/4	5/4
Females - Vessel injection slightly above normal	0/0	0/0	0/0	0/0	0/0	0/0	11/5	9/5

Current reviewer's comments: *Dr Lansita's referred to a separate ophthalmology report written by Terah Webb, DVM, Diplomate American College of Veterinary Ophthalmologists. Dr. Webb recommended that follow-up studies could be done to understand the corneal lesions and could include more detailed histopathology of the corneal lesions rather than a generalized histopathologic evaluation. Dr Lansita also listed the major conclusions of this ophthalmology report on her review with focuses in the corneal opacities.*

No treatment related changes in intraocular pressure were seen.

Hematology (Prestudy and Day 29)

Slight decreases in red blood cells, hemoglobin and hematocrit were seen on Day 29 in treated animals. A dose response was seen in females but not males. The decreases were generally within the historical control range. The Applicant attributes the

decreases to the higher number of TK samples (9 TK samples) collected in treated animals compared with 1 TK sample from control animals.

Clinical Chemistry (Prestudy and Day 29)

No test article-related effects

Urinalysis (Day 29)

No test article-related effects

Gross Pathology

Male R3240 treated with 2.0% phentolamine mesylate showed bilateral opacification of the vitreous. The study report claims that a microscopic correlate was not seen for this lesion. However, based on the ophthalmology report it is not clear that the specific area of the opacity was evaluated microscopically. This observation may indicate an intraocular change. Dark foci that correlated microscopically with focal ulceration of the mucosa with were seen in the stomach mucosa in 2 males at 0.5% and 1 male at 2.0%. One male at 2.0% (R3251) had an epididymal cyst that correlated with a dilated lymphatic.

Current reviewer's comments: *On 31 August 2011, FDA asked for comment on the significance of the bilateral vitreous opacification observed on gross necropsy in animal No. R3240. On 18 October 2019, the Applicant provided a memo in the IND Annual Report (SDN-23). The memo states that examination of the original eye blocks (blocks 23 and 26) by Dr. Michelle Elliott on 07-AUG- 2018 showed complete filling of the posterior segment of each globe with paraffin wax, confirming that the vitreal matter had been lost during processing. Given the loss of the vitreous during processing, the current memo concludes that further sectioning of the blocks is not recommended as it will not give any further information regarding the described opacification.*

Organ Weights

No test article related changes were seen in organ weights. A statistically significant increase in testes (2.0% males) and kidney weights (1.0% and 2.0% males) was seen that was not correlated with histopathologic findings.

Histopathology (Full tissues from control and high-dose groups; eyes, eyelids, lacrimal glands, and optic nerved from all groups)

Adequate Battery – No, in future studies, the Applicant should microscopically evaluate the corneal opacities rather than a general area that may not include the opacity.

Peer Review - No

Histological Findings

No test article-related adverse changes were seen.

Two males at 2.0% showed epididymal vacuolation *(mild to moderate)* with no changes to the testes. Fatty infiltrates of the thymus were seen in 2.0% treated animals *(mild to marked)* compared with controls *(mild to moderate)*. One 2.0% animal showed a focus of gastric ulceration that correlated with a macroscopic finding of dark foci; the Applicant notes that "such ulcerative changes are not uncommon in rabbits and may be associated with stress." It is unclear whether these changes are related to test article or not since they were seen in a few animals with no clear adverse outcome. These findings should be followed for progression in future studies.

Toxicokinetics (Days 1 and 28 at predose and 2 to 8 hours post 1st dose)

The systemic TK of phentolamine mesylate was measured from plasma samples. The TK results are summarized in Table 8. The mean T_{max} was 0.25 hours across dose groups on Days 1 and 28 following the last dose administration. The mean $T_{1/2}$ ranged from 0.897-1.16 hours on Day 1 and from 0.833-1.36 hours on Day 28 across dose groups. A gender difference was observed with females showing greater C_{max} (1.4 to 3.3-fold) and AUC (1.4 to 2.0-fold) values than males on Day 1 and Day 28; the higher exposure in females likely correlates with the greater incidence and severity of the observed ocular conjunctivitis and corneal opacities in females compared with males.

Table 8: Summary of Exposures in Male and Female Rabbits following Topical Ophthalmic Administration of Phentolamine Mesylate 4 Times per Day for up to 28 Days

Dose (ug/day)	Day 1 Cmax		Day 28 Cmax		Day 1 AUC		Day 28 AUC	
	Males	Females	Males	Females	Males	Females	Males	Females
1600/0.5%	3300	7220	3980	10300	5400	9310	7600	13100
3200/1.0%	4780	8550	3950	13100	9910	14300	8680	17800
6400/2.0%	19300	46800	17000	24200	35200	67200	26800	49300

Slight accumulation was observed between Day 1 and Day 28 for C_{max} (1.2-1.5-fold) and AUC (1.2-1.4-fold) at the 0.5% (males and females) and 1.0% (females only) dose groups.

Dosing Solution Analysis

Dosing solutions ranged from 85.6% to 96.3% of nominal concentration. Samples below 10% of nominal concentration included some low dose samples (middle sample; 85.6% to 87.9%) and mid-dose sample with a value 88.9% nominal. Additional results presented for the low dose group were within 10% of nominal.

7 Genetic Toxicology

No genotoxicity studies were conducted by the Applicant. The Applicant intends to rely on the mutagenicity information reported in Section 13.1 of the approved product labeling for OraVerse® (Septodont Holding, 2016).

8 Carcinogenicity

No carcinogenicity studies were conducted by the Applicant and no carcinogenicity studies were conducted for the approval of OraVerse® (Septodont Holding, 2016) or for Regitine® (Novartis Pharmaceuticals Corporation, 1998) upon which the Applicant intends to rely.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted by the Applicant. The Applicant intends to rely on the information reported in Section 8.1 and Section 13.1 of the approved product labeling for OraVerse® (Septodont Holding, 2016) and in the Pregnancy section of the approved product labeling for Regitine® (Novartis Pharmaceuticals Corporation, 1998).

10 Special Toxicology Studies

Ocular Toxicity Studies on Impurities – A 5-Day Repeat Dose Tolerability Study in Dutch-Belted Rabbits (Study No. 20011929; Module 4.2.3.7.6) - Male rabbits were treated with either Phentolamine Ophthalmic Solution (POS) or POS spiked with (b) (4) % (b) (4) after for 5 days as shown in the table below. The concentration of POS was 1% as the mesylate salt or 0.75% as phentolamine. Two drops per eye (separated by 5 minutes) were administered on each dose interval twice daily (8 hours apart) for a total of 4 drops/eye/day.

Table 9: Study Design – 5-Day Ocular Tolerability Study to Qualify (b) (4)

Group	Treatment	Conc	Dose Regimen	#Drops/ eye/ interval[1]	# of drops/ eye/day	Drop vol.[2]	Dose/ eye/day	# Animals M
1 (Control)	POS	PA: 7.5 mg/mL (b) (4)	BID[4] OU	2	4	(b) (4) µL	PA: 1.05 mg (b) (4)	5
2 (Test)	POS + (b) (4) % (b) (4)	PA: 7.5 mg/mL (b) (4)	BID[4] OU	2	4	(b) (4) µL	PA: 1.05 mg (b) (4)	5

Abbreviations: BID = twice daily; Conc – concentration; M – male; PA – phentolamine; OU = both eyes.

[1] At each dose interval, each eye received a total of two drops, administered approximately 5 minutes apart.
[2] Dosed using a calibrated micropipette.
[3] Target levels of (b) (4) see Attachment 3: Drug Formulation Analysis Report for reported levels. No correction was applied for amount of (b) (4) in the Test Formulation.
[4] Dosing at 8:30 and 16:30 (± 30 minutes)

Source: Study Report Chart 3

Note: The values under column "dose/eye/day" appeared to have used a drop volume of (b) (4) µL instead of the (b) (4) µL shown in the table. The unit under column "dose/eye/day" is not correct, it should be mg instead of mg/mL.

Evaluations of toxicity included mortality, clinical observations, body weights, ocular irritation (Draize score), ophthalmic examinations (slit lamp with fluorescein staining, indirect ophthalmoscopy), ocular health evaluations, and IOP measurements. After the completion of the ophthalmic examinations on Day 5, the animals were euthanized and the ocular tissues (eyelids, globes with optic nerve, Harderian gland, lacrimal gland, nictitating membranes) were preserved but not evaluated.

Key findings:

- No adverse ocular findings were observed after administration of POS alone or spiked with (b) (4) % (b) (4) based macroscopic (Draize) evaluations, slit lamp evaluations, indirect ophthalmoscopy (fundus exams), and IOP measurements.
- Mild conjunctival congestion (score 2) was occasionally observed across both groups, but there was higher incidence in eyes treated with POS + (b) (4) However, the findings were transient and did not persist with continued dosing. This congestion is expected based on the alpha-adrenergic pharmacology of phentolamine (vasodilation).
- Histopathology evaluation of ocular tissues was not conducted. However, based on the lack of adverse findings by ophthalmic evaluations and the intended short-term use for marketing (a total of 1 to 2 drops), the evaluation

performed is considered sufficient to qualify [redacted] (see calculations below). If a future application seeks a longer-term indication, additional studies may be needed to qualify this impurity at a specification of NMT [redacted]%.

Calculations to determine qualification:

- The maximum intended marketing daily dose of phentolamine 0.75% is [redacted] mg/eye/day ([redacted] mg/mL phentolamine X [redacted] µL X 2 drops).
- At a specification on NMT [redacted]% for [redacted] the total daily dose of the impurity is [redacted] mg/eye/day [redacted] mg/eye/day X [redacted])
- Four drops of [redacted] at [redacted]% [redacted] mg/eye, per Table 9 above) in the current study provides an exposure margin of 2.6X the proposed specification of [redacted]% in the drug product [redacted] mg/day).
- The specification is considered qualified for ocular safety.

To support systemic safety, the Applicant referred to the publication by [redacted] Dogs received phentolamine alone or in combination with [redacted] and another impurity [redacted] [redacted] (referred to as [redacted] in the publication) was evaluated at dose levels of [redacted] µg/kg after an intraoral single dose or repeated doses on Days 1, 8, and 15. Each dog received treatment in 1 right maxillary quadrant and in 1 right mandibular quadrant. Per information in the publication, the study was conducted under GLP regulations. The standard parameters of a general toxicity study were evaluated (clinical signs, body weights, food consumption, hematology, clinical chemistry, gross necropsy, organ weights, and histopathology). In addition, evaluations included heart rate, body temperature, respiration, gait, and disposition. No adverse findings attributed to the test articles were observed.

The systemic exposure margins, per the Applicant's calculations (see Table 9 in NDA Module 2.6.6 Toxicology Written Summary), are 9X (adult dose of 2 drops) and 6X pediatric dose of 1 drop), assuming 100% systemic absorption. However, after correcting to HED, the exposure margins are 5X and 3.3X, respectively. Because of the short-term dosing (maximum of 1 or 2 drops), there is minimal concern for adverse findings related to the impurity to occur in humans.

It was stated in the publication that [redacted] and [redacted] were neither genotoxic nor clastogenic in genetic toxicity studies [redacted] unpublished data).

11 Integrated Summary and Safety Evaluation

Ocuphire is pursuing a 505(b)(2) regulatory pathway, with OraVerse® (phentolamine mesylate, 0.4 mg/1.7 mL solution per cartridge) and Regitine®

[redacted]

(phentolamine mesylate for injection) as the LDs. The Applicant conducted original ocular nonclinical studies to support the ophthalmic indication and formulation. The studies included a 5-day non-GLP ocular tolerability study, topical ocular GLP studies with dosing for 28 days and 6 months, and a 5-day topical ocular tolerability study to support the specification of a major impurity. In all studies, there was an exaggeration of the intended clinical regimen for reversal of mydriasis by concentration, daily dosing frequency, and/or duration of dosing. In the 2 GLP ocular toxicity studies and the impurity qualification study, the formulation was representative of the commercial Phentolamine Ophthalmic Solution 0.75% formulation.

Based on the intended dosing regimen of a total of 1 to 2 drops, only the 5-day non-GLP and 28-day GLP studies were reviewed to support this NDA. The 5-day study to qualify (b) (4) was also reviewed. The main findings include:

5-Day Non-GLP Rabbit Study:

- Ocular administration of phentolamine mesylate ((b) (4) µL/dose) BID for 4 days and QID for 1 day was well tolerated in rabbits at concentrations of 0.5%, 1.0%, and 1.5%. There were no ocular findings.
- Ocular administration of phentolamine mesylate QID for 3 days at 2.0% resulted in slight conjunctival redness, swelling, and discharge.
- Administration at a concentration of 5.0% was considered overtly irritating to the eye and would not be suitable for longer-term studies.
- The NOEL for short-term exposure (1-to-4-day treatment) was 1.5% BID (4 days) or 1.5% QID (1 day).
- The NOAEL for short-term exposure (1 to 3 days treatment) was 2% QID.

28-Day GLP Rabbit Study

- The main study findings include conjunctivitis (redness, swelling and discharge), ocular surface hyperemia (slight), and corneal opacities (involving <25 to 75% of the cornea) observed mainly in the 2.0% QID dose group. The discharge severity score ranged from 1 to 2 indicating above normal to abundant discharge. These findings were not associated with adverse microscopic findings.
- No adverse intraocular or systemic changes were observed.
- Slight transient conjunctival redness was considered related to the pharmacological activity of phentolamine as an alpha-adrenergic antagonist.
- Based on the mild to moderate corneal opacities, macroscopic irritation (conjunctivitis) and increased ocular surface hyperemia at 2% QID, the NOAEL was 1.0% QID.

Exposure margins resulting from these findings are shown in the table below. The nonclinical data support the ocular safety of the dosing regimen intended for marketing.

Table 10: Exposure Margins for Total Ocular Dose in Adults and Children

Study	Key Findings	NOAEL	Exposure margins at MRHOD (2 drops adults; 0.6 mg/eye 1 drop children (0.3 mg/eye/day)
5-day rabbit	No findings at ≤1.5% BID for 4 days or ≤1.5% QID for 1 day (NOEL) Slight redness, swelling and discharge at 2% QID for 3 days (NOAEL) Severe irritation at 5% QID	2.0% QID 4 mg/eye	6.7X (adults) 13X (children)
28-day rabbit	Isolated occurrences of conjunctival redness and discharge, and corneal opacity (involving < 25% of the cornea) (NOAEL) at ≤1% QID Conjunctivitis (redness, swelling and discharge), ocular surface hyperemia (slight), and corneal opacities (involving <25 to 75% of the cornea) mainly at 2.0% QID	1% QID 1.6 mg/eye	2.7X (adults) 5.3X (children)

Calculations based on phentolamine mesylate. The clinical formulation of 0.75% phentolamine is equivalent to 1% phentolamine mesylate.
Drop volume of (b) (4) µL (5-day rabbit study), (b) (4) µL (28-day rabbit study), and (b) (4) µL in humans.

5-Day (b) (4) Qualification Study

The proposed shelf-life specification for (b) (4) in Phentolamine Ophthalmic Solution is not more than (b) (4) % phentolamine ((b) (4) mg/mL in Phentolamine Ophthalmic Solution) which is above the qualification limit of (b) (4) % for identified impurities per ICH Q3B(R2) Impurities in New Drug Products.

Phentolamine Ophthalmic Solution 0.75% spiked with (b) (4) % (b) (4) was well-tolerated based on clinical observations, ocular irritation (Draize score), ophthalmoscopy and IOP measurements when administered BID (2 drops per interval) to DB rabbit eyes for 5 days. Histopathology evaluation of ocular tissues was not conducted. However, based on the lack of adverse findings by ophthalmic evaluations and the intended short-term use for marketing (a total of 1 to 2 drops), the evaluation performed is considered sufficient to support the ocular safety of (b) (4) at the proposed specification.

The published dog study performed for OraVerse® (b) (4) assessed the systemic toxicity of (b) (4) after intraoral injection in dog (single and repeat dose) and provides support for the potential systemic exposure to (b) (4) The resulting exposure margins from this study are at least 5X and 3.3X the maximal recommended dose in adults and children, respectively, based on body surface area. Because of the short-term dosing (maximum of 1 or 2 drops), there is minimal concern for adverse findings related to the impurity to occur in humans.

The proposed specification of (b) (4)% is considered qualified.

Bridge to Support Systemic Safety based on LD

To support this 505(b)(2) NDA, the Applicant is relying on the Agency's previous findings of nonclinical systemic safety, clinical pharmacology, and systemic clinical safety for the approved listed drugs (LDs), Regitine® (NDA 008278) and OraVerse® (NDA 022159), in addition to Applicant-conducted studies, and information available in the published literature. To enable reliance on the proposed LDs, the Applicant believes they have established a scientific bridge through demonstration of lower systemic phentolamine exposure from the Phentolamine Ophthalmic Solution 0.75% product compared to clinical data in the published literature (Moore et al. 2008) for OraVerse®.

The Applicant states that pharmacokinetic analysis based on data collected in the OPI-NYXRM-302 (MIRA-3) study showed that phentolamine exposure following a total dose of 0.9 mg phentolamine mesylate (three 0.03 mL drops of Phentolamine Ophthalmic Solution at 10 mg/mL phentolamine mesylate concentration) is below the exposure reported in the literature and the OraVerse® label for phentolamine mesylate dosed via the intraoral submucosal route at concentrations ranging from 0.4 mg to 0.8 mg phentolamine mesylate (Table 11). The intended maximum dose for Phentolamine Ophthalmic Solution 0.75% is 2 drops per eye; based on dose linearity, exposures associated with 4 drops are also below reported phentolamine exposures. The safety window is wider compared to oral administration of phentolamine mesylate formulations referenced in Silva et al. with a C_{max} of 11.52 and 12.21 ng/mL and an estimated AUC_{0-3h} of 20.62 and 21.60 ng•hr/mL.

Table 11: Mean Phentolamine PK Parameters From OPI-NYXRM-302 (MIRA-3) Clinical Study and Literature Data

Source	Route of Administration	PAM Dose (mg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-3h} (hr*ng/mL)	T_{last} (hr)
Ocuphire OPI-NYXRM-302 (MIRA-3) [3 drops as administered][a]	ophthalmic	0.9 (3 drops)	0.53	0.25	0.98	3
Ocuphire OPI-NYXRM-302 (MIRA-3) [estimated PK for 4 drops] [a]	ophthalmic	1.2 (4 drops)	0.71	0.25	1.31	3
Lin et al. 2018[b,c]	intraoral, submucosal	0.2	0.71	0.09	0.71	15
			0.70	*0.22*		
	intraoral, submucosal	0.4	1.28	0.11	1.37	15
			1.34	*0.21*		
OraVerse Moore et al. 2008 (NOVA 04-PK)[b,c]	intraoral, submucosal	0.4	1.39	0.28	2.31	8
			1.34	*0.25*		
	IV	0.4	10.99	0.02	3.01	8
			10.98	*0.12*		
Lin et al. 2018[b,c]	intraoral, submucosal	0.8	2.55	0.09	2.69	15
			2.71	*0.20*		
OraVerse Moore et al. 2008 (NOVA 04-PK)[b,c]	intraoral, submucosal	0.8	2.68	0.17	3.59	8
			2.73	*0.18*		
Silva et al. 2004[b,c]	oral, Reference formulation 1	40	12.21	0.83	21.60	12
			15.40	*0.83*		
	oral, Reference formulation 2	40	11.52	0.67	20.62	12
			14.20	*0.67*		

C_{max}=maximum plasma concentration; T_{max} = time to reach maximum concentration; T_{last} = time to last observable concentration; AUC = area under the curve; NA = not applicable; NC = not confirmed; PAM = phentolamine mesylate; PK = pharmacokinetic

[a] The noncompartmental PK modeling data for C_{max} and AUC_{0-3h} are presented as geometric mean and for T_{max} as median value, and extrapolated for 4 drops.

[b] Literature PK data are calculated based on digitized mean PK concentration data

[c] Data marked in *Italics* are based on the PK parameters reported in Silva 2004, Moore 2008 and Lin 2018 based on the individual PK concentrations. Other data are based on the current analysis of the Applicant-conducted OPI-NYXRM-302 (MIRA-3) study and literature data (digitized mean PK profiles).

Source: Sponsor's Table 6, Module 2.7.2, Summary of Clinical Pharmacology, page 11

Based on these data, it is the Pharmacology/Toxicology team's perspective that the Applicant has demonstrated an adequate bridge. However, the final decision is under the purview of the clinical and clinical pharmacology review teams.

Conclusion and Recommendations:

Overall, the nonclinical data presented in this NDA provides adequate safety support for the approval of Phentolamine Ophthalmic Solution 0.75% at the intended marketing dosing recommendation of 1 or 2 drops in the reversal of mydriasis. Pharmacology/Toxicology team recommends approval.

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/s/

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