CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 REVIEW AND EVALUATION

Application number:	215352
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Applicant's letter date:	SD # 1: 12-28-2020
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Product:	Tropicamide 1%/ Phenylephrine 2.5%
	Ophthalmic Spray (MYDCOMBI™)
Indication:	Mydriasis in routine diagnostic procedures and in conditions where short-term pupil dilation is desired
Applicant:	Eyenovia
Review Division:	Division of Ophthalmology
Reviewer:	María I Rivera, PhD, DPT-RPURM/SM
Supervisor/Team Leader:	Lori E Kotch, PhD, DABT, DPT-RPURM/SM
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Template Version: September 1, 2010

Disclaimer

Any information or data necessary for approval of NDA 215352 that Eyenovia does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 215352.

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1 Executive Summary

1.1 Introduction

Eyenovia is seeking approval for the marketing of Tropicamide 1%/Phenylephrine Hydrochloride 2.5% Ophthalmic Spray (MYDCOMBI™) fixed combination product for use in pediatric and adult subjects needing mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired. The ocular safety of tropicamide and phenylephrine is well established, with a long history of safe use as individual agents and with coadministration as the standard of care for mydriasis in the U.S. and as an approved fixed combination product in multiple countries worldwide.

The formulation of topical tropicamide and phenylephrine hydrochloride in Eyenovia's fixed combination product is very similar to the commercial products. The inactive ingredients are known to be safe when used clinically in ocular formulations. The drug product is delivered using the Eyenovia's Optejet Dispenser resulting in a total topical ocular dose lower than that applied topically by the solutions in drop form.

Eyenovia is seeking approval of this product through submission of a 505(b)(2) NDA. The nonclinical support relies on the Agency's previous finding of nonclinical safety for the following applications:

- NDA 012111, Tropicamide Ophthalmic Solution USP (MYDRIACYL), 0.5% and 1%, from Alcon (Alcon, 2019)[1]
- NDA 207926, Phenylephrine Hydrochloride (PE-HCl) Ophthalmic Solution, 2.5% and 10% from Akorn Inc. (Akorn, 2019)
- NDA 022565, Ibuprofen 200 mg/Phenylephrine 10 mg oral. Advil Congestion Relief Tablets™ from Wyeth Consumer Healthcare (Wyeth Consumer Healthcare, 2020)

In addition, Eyenovia relies on the published literature and the long clinical history of safe and effective ophthalmic use of both active ingredients used individually or in combination. The bridge to support reliance is based on the smaller total daily dose resulting from MYDCOMBI™ compared to the drop formulations.

1.2 Brief Discussion of Nonclinical Findings

No original nonclinical studies were submitted to support the safety of the combination. The nonclinical support is primarily based on published literature for each individual active component. From a nonclinical perspective, administering a lower dose (in a smaller volume) raises no new safety concerns for topical ocular phenylephrine or tropicamide compared to approved topical ocular drugs. Given the existing clinical

[1] The MYDRIACYL label being included in this NDA is designated as "Alcon, 2019" (ANDA 084306); the MYDRIACYL product under NDA 012111 was discontinued by Alcon but not for reasons of safety or effectiveness.

experience with both tropicamide 1% and phenylephrine hydrochloride 2.5% used individually or in combination at the intended dosing regimen, and the use of common ocular excipients in the clinical formulation, there are no specific nonclinical concerns regarding the approval of this NDA.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

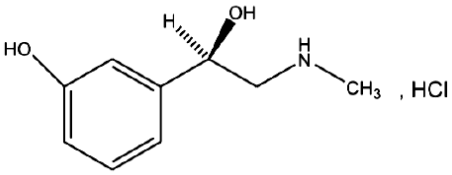
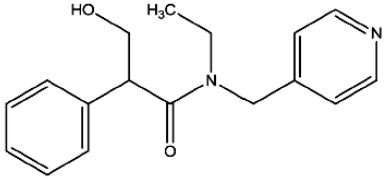
(b) (4)

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

(b) (4)

2 Drug Information

2.1 Drug

Attribute	Phenylephrine	Tropicamide
CAS Registry Number (Optional)	61-76-7	1508-75-4
Generic Name	Phenylephrine Hydrochloride	Tropicamide
Code Name	P70, PEH	1030
Chemical Name	Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, hydrochloride (R)-. ( )-m-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride. (1R)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol hydrochloride	Benzeneacetamide, N-ethyl-α-(hydroxymethyl)-N-(4-pyridinylmethyl)-, (±)- (±)-N-Ethyl-2-phenyl-N-(4 pyridylmethyl)-hydracrylamide or N-ethyl-3-hydroxy-2-phenyl-N-(pyridinylmethyl)propanamid
Molecular Formula/Molecular Weight	$C_9H_{13}NO_2$.HCl/203.67 g/mol	$C_{17}H_{20}N_2O_2$/284.35 g/mol
Structure or Biochemical Description		
Pharmacologic Class	α-adrenergic receptor agonist	muscarinic receptor inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 135936 (submitted 10-9-2018) – Eyenovia's Phenylephrine 2.5%/Tropicamide 1% Microdose Ophthalmic Solution administered by the Eyenovia's MicroDose Dispenser (MiDD)
- DMFs (b) (4)
- Listed drugs:
  - NDA 207926, Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% and 10% (Akorn, 2019)
  - NDA 022565, Ibuprofen 200 mg/Phenylephrine 10 mg oral. Advil Congestion Relief Tablets™ from Wyeth Consumer Healthcare (Wyeth Consumer Healthcare, 2020)
  - NDA 012111, Tropicamide Ophthalmic Solution USP (MYDRIACYL), 0.5% and 1%, from Alcon (Alcon, 2019)

2.3 Drug Formulation

MYDCOMBI (tropicamide 1% and phenylephrine hydrochloride 2.5%, Ophthalmic Solution) is a sterile (b) (4) solution of tropicamide and phenylephrine. Table 1 provides the composition of the solution.

Table 1: Composition of MYDCOMBI (Tropicamide 1% and Phenylephrine Hydrochloride 2.5%,) Ophthalmic Solution

Ingredient	Function of Components	Quality Standard	Concentration (w/w %)	Amount (mg/mL)
Phenylephrine HCl	Active	USP	2.5	25
Tropicamide	Active	USP	1.0	10
(b) (4)® Benzalkonium Chloride (b) (4)	Preservative	USP/NF	0.01	0.1
Hydrochloride Acid and/or Sodium Hydroxide	pH adjustment	USP/NF	As needed for pH adjustment to 5.0±0.2	As needed for pH adjustment to 5.0±0.2
Water for Injection	(b) (4)	USP	q.s.	q.s.

NF = National Formulary; q.s. = quantum satis; USP = United States Pharmacopeia

MYDCOMBI is provided in an Optejet dispenser that is composed of two interdependent components, the base unit and the cartridge. The cartridge and base unit are designed to deliver a microdose (8 µL) of an ophthalmic formulation (b) (4) using (b) (4) microdroplets to coat the ocular surface.

2.4 Comments on Novel Excipients

The drug product contains no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

The CMC team requested Pharm/Tox team input on the safety of three leachables identified above the analytical evaluation threshold: [redacted] and [redacted] (the latter 2 were not differentiated by the analytical method). These leachables were detected in the container closure system. The Sponsor provided a toxicological evaluation performed by a consultant ([redacted] to support ocular and systemic safety for these three leachables. The evaluation was submitted under SD # 13 (5-25-2021).

In performing the hazard assessments, the consultant conducted a search of the readily available open literature. The toxicity of the leachables was assessed in two ways: (1) potential systemic toxicity due to administration of the drug product containing these drugs occasionally or infrequently on an acute basis; and (2) potential for local effects on the eye due to low concentrations in the drug product.

The consultant calculated Permitted Daily Exposure (PDE), the maximum levels detected and margins of safety for systemic exposure are shown in the following table:

Leachable Impurity	Maximum concentration detected	Maximum Administered Dose (systemic)	Systemic PDE	Margin of Safety
[redacted]				

Maximum Administered Dose is based on 2 sprays per eye (8 µL/spray) and bilateral administration (total of 4 sprays)
Margin of safety assumes 100% of the ocular dose is absorbed.

The high exposure margins for each leachable support no safety concerns for adverse systemic findings. Further details for PDE calculations and determination of ocular safety are given below.

[redacted]

Some excerpts from the consultant report are:

- Both [redacted] and [redacted] are commonly found in foods.
- While [redacted] appears in many assessments for groups of similar compounds, data specific to [redacted] alone were not identified. [redacted] has been well characterized.
- Estimated daily exposure (single portion exposure technique or SPET) of [redacted] µg/day has been reported for [redacted] (apparently characterized in a group of similar compounds); safe oral doses for [redacted] ranged from [redacted] mg/kg/day).

- [redacted] and [redacted] has many of the same physical and chemical characteristics and could not be differentiated in the leachables study.
- As the [redacted] and [redacted] share the same chemical features and functional groups (see Table 3.1 on page 5 of consultant report), it is reasonable to base the assessment of [redacted] on [redacted] is sometimes misidentified as [redacted]
- [redacted] was non-irritating in an ocular irritation assay conducted in rabbits, when instilled neat at a volume of [redacted] µL[2].
- Companies submitting information in support of [redacted] but did not supply supporting information. No publicly available eye irritation studies were identified.
- No evidence of genotoxicity was observed for [redacted] in bacterial reverse mutation (Ames) and L5178Y mouse lymphoma assays[2]. In vitro chromosome aberration (without S9 fraction) and sister chromatid (with S9 fraction) assays produced ambiguous results. In vivo micronucleus assays at up to [redacted] mg/kg were negative as was an unscheduled DNA synthesis assay in primary rat hepatocytes. A dominant-lethal assay at up to [redacted] mg/kg was negative.

The consultant calculated a PDE of [redacted] mg/kg, based on rat developmental toxicity NOAEL of [redacted] mg/kg/day (lowest NOAEL from all studies identified in literature), interspecies differences factor of 5 and intraspecies differences factor of 10.

3.7.3. Calculation of PDE

$$PDE = \frac{POD}{F1\text{-}5 \times \alpha \times MF}$$

PDE = [redacted]

PDE = [redacted] mg/day (rounded to one significant figure)

The consultant conclusion was the following:

"The maximum concentration of [redacted] *identified in the container closure system was* [redacted] *ng/µg). Assuming a maximum daily dose of two sprays of 8 µL/spray, in each eye, this would correspond to a maximum daily dose of* [redacted] *× 8 µL/spray × 2 sprays/eye × 2 eyes). Even assuming that 100% of an ocular dose was absorbed systemically, this is well below the calculated PDE of* [redacted]

[2]European Chemicals Agency (2021). REACH Registration Dossier for: Bis(2-ethylhexyl) adipate. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15293. Accessed May 2021.

mg/day for systemic effects for (b) (4) *and even below the estimated daily intake of* (b) (4) *µg/day for* (b) (4) *in foods.*

For assessing the potential for (b) (4) *to cause local effects on the eye, studies with* (b) (4) *indicated that it is not a skin or eye irritant. Assuming a worst-case scenario in which the* (b) (4) (b) (4) *leachable identified was actually* (b) (4), *and assuming* (b) (4) *was a Category 2 eye irritant in the GHS system, a solution containing* (b) (4) *of a GHS Class 2 eye irritant would not be considered an eye irritant*[3]*. However, given the similarity between* (b) (4) *(which has been tested and found to be non-irritating) and* (b) (4) *it is considered unlikely that* (b) (4) *is actually an eye irritant."*

To search for additional information regarding local effects in the eye, this reviewer conducted an online search and found the following publication: (b) (4), the following is stated:

(b) (4)

Thus, per this publication, (b) (4) is not an eye irritant. Thus, this reviewer believes that the information presented by the consultant, in addition with this published report, support no systemic or ocular safety concerns for either (b) (4) or (b) (4) at the levels found in the container closure system. As a note, the proposed label indicates a maximum of 3 sprays in children less than 1 year of age (vs 2 sprays used by the consultant in this assessment), but this discrepancy has no significant impact on these conclusions.

(b) (4)

(b) (4)

Some excerpts from the consultant report are:

- Sufficient data on (b) (4) were not available to develop a compound specific PDE, and therefore the recommended PDE was based on data available for its parent compound, (b) (4)
- (b) (4) (see structures on page 10 of consultant report).
- Both forms have been found in surveys of environmental pollutants and indoor dust. No specific standards for either (b) (4) or (b) (4) were identified.
- (b) (4) was not an eye or skin irritant in rabbits[4].
- (b) (4) was not genotoxic in vitro (Ames bacterial mutation assay, yeast mutation assay) or in vivo (chromosomal aberration assay in mouse spermatocytes, Chinese hamster bone marrow test)
    - *Consultant provided reference link (reference 39) could not be accessed.*
    - *Under consultant reference 37 (ref 5 below), the following is stated:* (b) (4)
- PDE Recommendations:
    - For (b) (4) a parenteral PDE of (b) (4) mg/day was recommended for parenteral exposures, based on the NOAEL identified in the 2-year rat feeding study (*carcinogenicity study*), and adjusting for 5% oral bioavailability[5]. The same publication recommended that in cases where a degradant was structurally similar to the parent compound and contained no additional structural alerts, the data of the parent compound may be used for risk assessment, as is the case for (b) (4) and (b) (4)
    - Therefore, the published PDE of (b) (4) mg/day is considered acceptable for systemic exposures to either (b) (4) or (b) (4)

Consultant conclusion:

"The maximum concentration of (b) (4) *identified in the container closure system was* (b) (4) *ng/µL). Assuming a maximum daily dose of two sprays*

(b) (4)

of 8 µL/spray, in each eye, this would correspond to a maximum daily dose of (b) (4) *× 8 µL/spray ×2 sprays/eye × 2 eyes). Even assuming that 100% of an ocular dose was absorbed systemically, this is well below the recommended PDE of* (b) (4) *mg/day for systemic exposures.*

In assessing the potential for (b) (4) *to cause local eye effects, data available on* (b) (4) *indicated that it is not an eye irritant, and furthermore,* (b) (4) *is not expected to be an eye irritant, particularly at such a low concentration* (b) (4) *in Client's ophthalmic drug product. Thus, the level of* (b) (4) *found as a leachable in the container closure system of Client's ophthalmic drug product is acceptable."*

This reviewer conducted an online search and found the following publication: (b) (4) "

In this publication, (b) (4)

This reviewer did not find any other published information on ocular effects for (b) (4) except for lack of ocular irritation reported in the (b) (4) Notwithstanding, this reviewer agrees with the consultant that the low level of (b) (4) µg/eye/spray) is of low concern given the topical ocular route of administration and short-term dosing frequency of 1 to 2 sprays (or up to 3 sprays in the proposed label for children less than 1 year of age) intended for this product.

In summary, this reviewer believes the available information support the levels of the three leachables do not pose significant ocular or systemic safety concerns.

2.6 Proposed Clinical Population and Dosing Regimen

- Pediatric and adult subjects needing mydriasis for routine diagnostic procedures and in conditions where short term pupil dilation is desired
- In patients 1 year of age or greater, administer one metered spray to the cornea. (b) (4)
- In pediatric patients less than 1 year of age, one metered spray should be administered as required, up to a maximum of 3 sprays per eye per day.

(b) (4)

2.7 Regulatory Background

- (b) (4)
- A Type B (Pre-IND 135936) meeting package was received on 8-18-2017. FDA conveyed preliminary comments on 9-12-2017. Nonclinical review was filed in DARRTS on 9-14-2017. The Sponsor cancelled the meeting after receiving the Division preliminary comments. The nonclinical team indicated that additional nonclinical studies are not anticipated to support the proposed Phase 3 trials or NDA submission, provided there are no issues with excipients or impurities that will need nonclinical qualification, and no reasons of concern arise in the clinical trials. The Sponsor was asked to provide a rationale in the NDA to support lack of concern regarding potential PK or toxicology interactions between active components, based on recommendations contained in the Guidance to Industry on "*Nonclinical Safety Evaluation of Drug or Biologic Combinations*." The Sponsor was also informed that the NDA should include all nonclinical elements (pharmacology, PK/ADME, ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicology, carcinogenicity, etc.).
- An End-of-Phase 2 supplement to Pre-IND 135936 was received on 6-5-2018. FDA provided preliminary comments on 7-16-2018. The Sponsor was reminded that for the listed drugs, they can rely only on the findings of safety and effectiveness (captured in the product labeling); FDA discipline reviews and summary basis of approvals (SBAs) cannot be relied-upon in a 505(b)(2) NDA application. Under the response to Question 1 (1st bullet), the microbiology review team recommended the Sponsor provide justifications and calculations for the proposed (b) (4) limits in the IND.
- Initial IND 135936 (SD # 7) received on 10-9-2018. Nonclinical review filed in DARRTS on 11-15-2018. No nonclinical studies were conducted with the combination. The nonclinical information was based on published literature. The decision to proceed was deferred to the medical team based on assessment of existing clinical experience.
- Pre-NDA Briefing Document (SD # 10) received on 4-18-2019. Nonclinical review filed in DARRTS on 5-14-2019. FDA provided written comments on 5-5-2019. Eyenovia canceled the sponsor meeting after receiving the preliminary comments. Nonclinical team agreed that additional nonclinical testing is unnecessary for a future NDA. The NDA will include biocompatibility data for fluid path components. The review of these type of studies is not under purview of Pharm/Tox (i.e., CDRH/devices generally reviews ISO-driven data).

Nonclinical team stated that if an expert level review of this material is needed, we defer to CDRH.

3 Studies Submitted

3.1 Studies Reviewed

No original studies were submitted/reviewed.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- Pre-IND 135936 nonclinical review (filed in DARRTS on 9-14-2017)
- Initial IND 135936 nonclinical review (filed in DARRTS on 11-15-2018)
- Pre-NDA nonclinical review (filed in DARRTS on 5-14-2019)
- NDA 207926, Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% from Akorn nonclinical review (filed in DARRTS on 12-8-2014)

4 Pharmacology

The pharmacological safety profile of phenylephrine and tropicamide after ocular administration are well known based on extensive clinical experience.

Phenylephrine is an α-adrenergic receptor agonist that has been used in the clinic since the 1930s to induce pupil dilation. When administered topically to the eye, phenylephrine constricts ocular blood vessels and stimulates contraction of the iris dilator muscle.

Tropicamide is a synthetic derivative of tropic acid that binds and blocks the action of muscarinic acetylcholine receptors, with anticholinergic activity similar to atropine, homatropine, and cyclopentolate. As a muscarinic cholinergic receptor antagonist, tropicamide has mydriatic and anti-accommodation properties that cause pupil dilation at lower doses and accompanied by cycloplegia at higher doses. When administered topically in the eye, tropicamide paralyzes both the pupillary sphincter muscle, causing pupil dilation, and the ciliary muscle that regulates accommodation.

The Applicant provided a review of the nonclinical literature for both phenylephrine and tropicamide. Some excerpts are presented below (references are included in the excerpts below as provided by the Applicant, but the complete citation is not included in this review):

Phenylephrine:

- Phenylephrine is a vasoconstrictor, and therefore decreases blood flow to the kidneys, viscera, limbs, and skin, while also decreasing intestinal motility (Eckstein & Abboud, 1962; Aviado, 1959). Coronary blood flow, however, is increased.
- At low doses, phenylephrine activates α-receptors. At higher doses, it acts as a weak agonist on β-receptors (Reinhardt & Wagner, 1974; Chiba, 1977). The stimulation of α1-receptors leads to vasoconstriction.
- The stimulation of α-receptors that are present on presynaptic nerve terminals generally blocks endogenous transmitter release.
- Activation of the α2-receptors that are located on cholinergic nerve terminals in the gastrointestinal tract reverses local inhibitory effects of α-agonists (Langer, 1977).

Tropicamide

- In rats, tropicamide 0.1% eyedrops induced marked pupillary dilation in treated eyes; the pupils of the contralateral, untreated eyes also dilate significantly, but less than the treated eyes (Patsiopulos et al, 2003).
- In cats, topical tropicamide 0.5% significantly elevated IOP in both the treated and untreated contralateral eye and caused pupil dilation in the treated eye, although no mydriasis was observed in the contralateral eye (Stadtbäumer et al, 2002, 2006).
- A single eyedrop of tropicamide 1.0% elevated IOP in dogs, in a breed-dependent fashion (Taylor et al, 2007). In dogs, ocular tropicamide 1.0% increased IOP by 8.8 ± 4.0 mmHg 35 minutes post-treatment in the treated eye but not the contralateral untreated eye; maximal mydriasis occurred at 55 minutes (Kovalcuka et al, 2017).
- In goats, topical tropicamide 1.0% produced rapid mydriasis (5-mm dilation within 30 min) that was maximal at 2 hours and recovered by 6 hours (Whelan et al, 2011).
- A single 50 µL topical dose of tropicamide 1.0% in 1 eye reduced tear production rates bilaterally in cats but had no effect on tear production in dogs. In cats, this effect was observed after 1-hour post-administration and recovered to baseline by 4 hours (Margadant et al, 2003).
- The effect in cats was dose-dependent, with 0.5% and 1.0% tropicamide solutions decreasing tear production by 72% and 95%, respectively, after 1 hour (Selk Ghaffari et al, 2016).
- Topical tropicamide administered to one eye in horses reduced tear production unilaterally (Selk Ghaffari et al, 2009).

4.1 Primary Pharmacology

Phenylephrine and tropicamide used in combination induce a mydriatic response, which is also demonstrated in nonclinical studies of phenylephrine and tropicamide administered to the eye as individual agents as noted above.

- In rabbits, topical administration of phenylephrine 2.5% with tropicamide 1.0% induced marked pupillary dilation compared to placebo controls (Lee et al., 1999).
- In rhesus and African green monkeys, phenylephrine 2.5% administered topically with tropicamide 1.0% induced statistically significantly greater pupil dilation than tropicamide 1.0% alone (Merrill and Burge, 2007).
- Increased pupil dilation was observed qualitatively in mice topically administered phenylephrine 2.5%, tropicamide 0.5%, or a combination of the 2 drug products (Mojumder, 2010).
- Topical administration of phenylephrine 5% with tropicamide 0.5% (prepared as hydrogel formulations) induced qualitatively increased pupil dilation in rabbits (Destruel et al., 2020).
- An ex vivo experiment using isolated porcine irides showed pupil dilation after administration of phenylephrine 2.5% and tropicamide 1.0% (Amini et al., 2012).
- The combination of phenylephrine 10% with tropicamide 1.0% did not induce a mydriatic effect in the pupils of horses (Hacker et al., 1987).
- No additional relevant pharmacology endpoints were evaluated in these studies.
- It is known that the co-administration of phenylephrine and tropicamide produces eye irritation such as burning, tearing, and stinging (Lee et al., 1999 and references therein).
- The drainage of both phenylephrine and tropicamide onto the nasal mucosa could result in systemic absorption of these two agents and produce many unwanted systemic side effects including tachycardia, hypertension, and headache (Lee et al., 1999 and references therein).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No nonclinical or clinical PK studies were conducted. The Division agreed (End of Phase 2 meeting held on 7-19-2018) that the collection of PK data for Eyenovia's dosage form (metered spray) was not needed, given the demonstrated systemic safety of the listed drugs. Eyenovia's outlined the following facts as the basis to conclude that the PK and safety data from the literature is adequate to support this NDA:

- The route of administration for Eyenovia's fixed combination product in spray form is the same as the listed drugs in drop form.
- Both active ingredients concentrations are the same as in the listed drugs (tropicamide 1% and phenylephrine 2.5%).
- No new excipients are being used in Eyenovia's fixed combination formulation.
- The total topical dose amounts of tropicamide 1% and phenylephrine 2.5% being administered by the Optejet dispenser (8 µL) are lower than those applied topically by the drop form (commonly, 25 to 50 µL).

- The exposure levels of the listed drugs in drop form are well characterized as being exceedingly safe and the exposure levels with Eyenovia's metered spray formulation would be inherently less than those of the listed drugs.

6 General Toxicology

Eyenovia cited 2 animal studies with phenylephrine and tropicamide used in combination but these studies were not specifically designed to assess toxicity. One in vitro combination study evaluated toxicity to corneal epithelial cells.

- **Hayasaka et al., 2003**[7] - Tropicamide 0.5% plus phenylephrine 0.5% did not induce aqueous flare elevation when topically administered to the eyes of rabbits (two 50 µL drops 30 minutes apart).
- **Li et al., 2019**[8] - Tropicamide 0.5% plus phenylephrine 0.5% did not induce lens opacity in mice (number of drops used is not clear but it is presumed 1 or 2 drops were instilled).
- **Destruel et al., 2020**[9] - Phenylephrine 5% with tropicamide 0.5% (prepared as hydrogel formulations), as well as solutions containing phenylephrine 5% with tropicamide 0.5%, PE 10% alone, and tropicamide 0.5% alone, induced a significant reduction (≥80%) in viability of human corneal epithelial cells compared to sodium chloride or hydrogel formulations alone (no phenylephrine or tropicamide) controls after incubation for 30 minutes, with no recovery after 24 hours of exposure in drug-free medium.

The nonclinical studies summarized by Eyenovia to support systemic safety of phenylephrine include the repeat-dose toxicity, genotoxicity, and carcinogenicity studies conducted by the National Toxicology Program[10]. These studies were also used for nonclinical support for the review of one of the listed drugs Eyenovia is relying on, i.e., NDA 207926, Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% from Akorn (see nonclinical review filed in DARRTS on 12-8-2014).

For tropicamide, Eyenovia indicated that limited reports were found in the literature. In rats, the reported oral LD_{50} of tropicamide is 865 mg/kg, the intraperitoneal

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[7] Hayasaka Y, Hayasaka S, Zhang XY and Nagaki Y. Effects of topical mydriatics and vasoconstrictors on prostaglandin-E2-induced aqueous flare elevation in pigmented rabbits. *Ophthalmic Res*. 2003, **35:** 256-260.

[8] Li XT, Qin Y, Zhao JY, Zhang JS. Acute lens opacity induced by different kinds of anesthetic drugs in mice. *Int J Ophthalmol*. 2019, **12:** 904-908.

[9] Destruel PL, Zeng N, Brignole-Baudouin F, Douat S, Seguin J. Olivier E, Dutot M, Rat P, Dufaÿ S, Dufaÿ-Wojcicki A, et al. In Situ Gelling Ophthalmic Drug Delivery System for the Optimization of Diagnostic and Preoperative Mydriasis. In Vitro Drug Release, Cytotoxicity and Mydriasis Pharmacodynamics. Pharmaceutics. 2020, **12(4)**: 360.

[10] National Toxicology Program Technical Report No. 322, Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride in F344/N Rats and $B6C3F_1$ Mice, NIH Publication No. 87-2578, January 1987, http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr322.pdf#search=phenylephrine%20hydrochloride

LD_{50} is 1210 mg/kg, and the subcutaneous LD_{50} is 872 mg/kg. In mice, the oral LD_{50} is 565 mg/kg, intraperitoneal LD_{50} is 695 mg/kg, and subcutaneous LD_{50} is 665 mg/kg.

Eyenovia did not find published information regarding potential mutagenicity and carcinogenicity of tropicamide, reproductive or developmental toxicity, or presence in the breast milk of lactating mothers.

7 Genetic Toxicology

Phenylephrine:

Eyenovia referred to studies conducted by the National Toxicology Program[10]. In these studies, phenylephrine was not mutagenic in Salmonella typhimurium (with or without S9 fraction). Mutagenicity assessments using the mouse lymphoma L5178Y/TK+/- assay were judged to be equivocal because the high doses of phenylephrine used were toxic to the cells and the results were not reproduced in a second study. A positive response was noted in the first trial without metabolic activation at the high dose of 1,500 µg/mL (relative total growth was 12.2%). Phenylephrine induced sister-chromatid exchange at ≥1500 µg/mL (-S9 fraction) but was negative for the formation of chromosomal aberrations in Chinese hamster ovary cells at doses up to 2,500 µg/mL (-S9 fraction) and 10,000 µg/mL (+S9 fraction).

Tropicamide:

Eyenovia did not find published studies for tropicamide.

8 Carcinogenicity

Phenylephrine:

Eyenovia made reference to carcinogenicity studies conducted by the National Toxicology Program[10]. Briefly, the carcinogenicity of phenylephrine was studied in two-year studies in mice and rats. The doses used were 0, 620, and 1,250 ppm phenylephrine in the diet in rats, and 0, 1,250, and 2,500 ppm in mice. There was no evidence of carcinogenicity in mice or rats. Based on the feed consumed, the maximum doses correspond to 50 mg/kg/day (rats) and 270 mg/kg/day (mice). The following non-neoplastic lesions were considered related to phenylephrine hydrochloride: chronic focal inflammation of the liver and perivascular cuffing of the lung at both doses in male and female rats, inflammation of the prostate at both doses in male rats, and focal cellular change in the liver in high-dose male mice.

In addition, phenylephrine hydrochloride is available under a variety of trade names as a solution for injection (10 mg/ml; max single dose is 1 mg IV), as tablets (10 mg), as various oral combination products (5-40 mg), and as various nasal spray solutions

(0.125%, 0.25%, 0.5%, and 1.0%)[11]. As a stand-alone product (e.g., Sudafed), the maximum recommended oral dose for adults is 60 mg/day (1 mg/kg based on a 60 kg body weight). Higher oral doses (80 mg/day or 1.33 mg/kg) are recommended in combination products (e.g., with guaifenesin). These doses are 66-fold the maximal recommended clinical dose, assuming 100% absorption after ocular administration (1.2 mg or 0.02 mg/kg based on 3 sprays/eye, 8 µL drop volume administered bilaterally).

Tropicamide:

Eyenovia did not find published studies for tropicamide.

Given the single day use of the intended product (1 spray at (b) (4) 5-minute intervals up to a maximum of 3 sprays per eye), lack of a reason for concern from the available genetic toxicity and carcinogenicity data, and/or long history of clinical use of phenylephrine or tropicamide, the inclusion of these data in the label is not considered clinically relevant in this case. This approach is consistent with other phenylephrine and tropicamide approved products for individual use.

9 Reproductive and Developmental Toxicology

Eyenovia cited two studies from the published literature conducted in pregnant rabbits or cultured chicken embryos.

- **Shabanah et al, 1969[12]** - Phenylephrine administered to pregnant female rabbits in the last third of their pregnancies (1 mg SC, 3X/day from GD 22 util delivery or from GD 16 on), resulted in reduced birth weight and early onset of labor.
- **Hodach et al, 1975[13]** – This study evaluated chick embryos for gross malformations and cardiovascular anomalies following a single in vitro treatment with L-phenylephrine (0.4×10^{-9} to 20×10^{-9} mol in 5 µL) on Day 5 of incubation. Following treatment, the eggs were examined after 24 hours for survivors, and then left undisturbed until Day 14 of incubation. Survivors were examined initially for gross evidence of external malformations and then examined internally for cardiovascular anomalies.

  Phenylephrine was lethal within the first 24 hours of treatment. A number of embryos that did not survive until Day 14 were not examined because of severe postmortem degeneration. The survival rate in phenylephrine-treated embryos decreased in a concentration-related manner (survival rate ≥66.1% vs 84.5% in saline control). Similarly, the percentage of embryos with cardiovascular

[11] Clinical Pharmacology Online Index (FDA Library)

[12] Shabanah EH, Tricomi V, Suarez JR. Effect of epinephrine on fetal growth and the length of gestation. *Surg Gynecol Obstet*. 1969, **129(2):** 341–343.

[13] Hodach RJ, Hodach AE, Fallon JF, Folts JD, Bruyere HJ, Gilbert EF. The role of beta-adrenergic activity in the production of cardiac and aortic arch anomalies in chick embryos. *Teratology*. 1975, **12(1):** 33–45.

anomalies increased in a concentration-dependent manner (8.1% to 19.2%, phenylephrine low dose to high dose vs 3.4% in saline control). The cardiovascular anomalies observed include anomalies of the aortic arches and ventricular septal defect.

Note: *It was incorrectly stated in Module 2.6.7 Toxicology Written Summary (page 6) that phenylephrine administration to chicken embryos did not cause any cardiac or external abnormalities. Also, the second citation for developmental effects in chicken embryos, i.e., Bruyere et al, 1983, did not evaluate phenylephrine.*

Eyenovia also stated the following:

"Administration of PE in human females in lunar months 1−4 of pregnancy was associated with an increase in minor malformations (including eye and ear) of the child (Heinonen et al, 1977). However, in 2 other studies, there were no associations between administration of PE during pregnancy and congenital abnormalities or disorders (Jick et al, 1981; Colley et al, 1982)."

Tropicamide:

Eyenovia did not find published studies for tropicamide.

Based on the lower drug volume administered with MYDCOMBI compared to approved ophthalmic phenylephrine and tropicamide products at same or higher concentrations and dosing regimens, the concern for reproductive toxicity is expected to be lower than that with the listed drugs.

10 Special Toxicology Studies

Module 4.2.3.6. Local Tolerance

The components of the microdose dispenser that provide the fluid pathway and that have direct contact with the drug product were evaluated for biocompatibility based on guidance provided in ISO 10993-1. The studies included cytotoxicity – MEM elution test, maximization test for delayed-type hypersensitivity in Hartley guinea pigs, and ocular irritation test in New Zealand White rabbits. Review of these type of studies is not under purview of Pharm/Tox (i.e., CDRH/devices generally reviews ISO-driven data). However, this reviewer has made an attempt to review this material and has concluded that none of these studies resulted in any finding of concern. If an expert level review of this material is needed, Pharm/Tox team defer to CDRH.

Biocompatibility Studies for the Microdose Dispenser

Test Name	ISO Number	Result	Supporting Documentation
Cytotoxicity – MEM Elution Test	ISO 10993-5:2009	Pass	(b) (4)
Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	ISO 10993-10:2010	Pass	
Ocular Irritation Test in New Zealand White Rabbits	ISO 10993-10:2010	Pass	

Additional studies included:

TR-17049 (Hypersensitivity testing in guinea pigs) and TR-17050 (Ocular irritation in rabbits) – These studies evaluated two new materials which are to be used in the (b) (4) i.e., parts that contact the drug directly) of the Optejet (b) (4) Cartridge:

(b) (4)

The results of both studies were negative.

11 Integrated Summary and Safety Evaluation

No nonclinical studies were conducted with the proposed combination product. The nonclinical support is primarily based on published literature for each individual active component.

The ocular safety of tropicamide and phenylephrine are well established, with a long history of safe clinical use alone or with co-administration as the standard of care for mydriasis in the US and as approved products in multiple countries. Phenylephrine

concentrations in FDA approved ocular products include 2.5% and 10%, whereas tropicamide concentrations include 0.5% or 1%. Dosing regimens include 1 drop every 3-5 minutes up to a maximum of 3 drops for 2.5% or 10% phenylephrine, and 1 to 2 drops with repetition at 5 minutes for 1% tropicamide. The intended dosing regimen for MYDCOMBI of 1 to 3 sprays is within approved dosing regimens for each individual active component.

Phenylephrine and tropicamide combination products are commercially available, although none have been FDA approved. A cursory online search by this reviewer identified marketed combination products with concentrations of 5% phenylephrine and 0.8% tropicamide (e.g., Tropicacyl Plus) and with the same concentrations as intended for MYDCOMBI, e.g., Phenylephrine 2.5 %-Tropicamide 1% from ImprimisRx®.

Eyenovia's rationale for product development was that topical ocular administration of a smaller volume of drug (8 µL) can "provide similar or superior efficacy to that administered with traditional eyedropper systems (commonly, 25 to 50 µL) while reducing systemic absorption and side effects." The use of the MicroDose Dispenser (MiDD) delivers a "controlled microdroplet spray of precise volume" to the tear film of the eye. From a nonclinical perspective, administering a lower dose (in a smaller volume) raises no new safety concerns for topical ocular phenylephrine or tropicamide compared to approved topical ocular drugs.

Given the existing clinical experience with both tropicamide 1% and phenylephrine hydrochloride 2.5% used individually or in combination at the intended dosing regimen, and the use of common ocular excipients in the clinical formulation, there are no specific nonclinical concerns regarding the approval of this NDA. Approval of this NDA is recommended.

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/

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