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APPLICATION NUMBER:

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PHARMACOLOGY 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

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SD # 8/ December 20, 2012

Product: Phenylephrine Hydrochloride Ophthalmic Solution
2.5% and 10%

Indication: Pupil dilation [REDACTED] (b) (4)

Applicant: Paragon BioTeck, Inc

Review Division: Transplant and Ophthalmology Products

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1 Executive Summary

1.1 Introduction

Phenylephrine is an α -adrenergic receptor sympathetic agonist that has been used for more than 70 years to dilate the pupil in ocular diagnostic, therapeutic and surgical procedures due to its vasoconstrictor and mydriatic action. In the eye, phenylephrine acts locally to constrict ophthalmic blood vessels and the radial muscle of the iris. Due to its long and established use phenylephrine hydrochloride has a status of GRASE (generally recognized as safe and effective) under the conditions specified in 21 CFR Part 341. An over-the-counter (OTC) monograph was developed for use as an ophthalmic vasoconstrictor for relief of ocular redness at concentrations between 0.08% and 0.2%. The phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, currently being used in the USA for mydriasis, are outside of the approved OTC monograph and are being supplied and used as unapproved products. Therefore, in this NDA, Paragon Biotech, Inc is seeking to market an FDA approved product for Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%.

This NDA is being submitted as a 505(b)2 application. The applicant relies on published literature and the Agency's findings of safety and effectiveness for NDAs 084-300, 007-953 and 22-565 for additional information on the clinical efficacy and clinical and non-clinical safety for phenylephrine hydrochloride not included in this application.

1.2 Brief Discussion of Nonclinical Findings

On the basis of the well established use of phenylephrine hydrochloride, the non-clinical safety information is largely based on the comprehensive toxicology testing conducted on phenylephrine hydrochloride by the National Toxicology Program in 1987. No new clinical or nonclinical studies were conducted.

In 12-week repeated-dose studies, the approximate lethal daily dose was 300 mg/kg for male rats and 1,400 mg/kg for male mice (139-fold and 334-fold, respectively, the recommended maximal ocular doses based on body surface area). Target tissues identified included the eyes in both species, the testes and seminal vesicles in male rats, and ovaries in female rats. At the no observed adverse effect level (NOAEL), the safety margins for these findings are at least 555-fold and 139-fold the recommended maximal ocular dose at 2.5% and 10%, respectively, based on body surface area.

Phenylephrine hydrochloride showed no evidence of carcinogenicity in rats or mice. Several non-neoplastic lesions considered related to phenylephrine hydrochloride were observed in the liver (both species), prostate (rats), and lungs (rats). Based on body surface area, the non-neoplastic findings in the rat (no NOAEL) were observed at 44-fold and 11-fold, the recommended maximal ocular dose at 2.5% and 10%, respectively. The NOAEL in mice was 122-fold and 31-fold the recommended maximal ocular dose at 2.5% and 10%, respectively.

Phenylephrine given to pregnant rabbits during the last third of gestation produced a decrease in fetal weight and the onset of early labor at a dose 3.69-fold and 0.93-fold the recommended maximal ocular dose at 2.5% and 10%, respectively.

In sheep, phenylephrine administered during the third trimester depressed uterine blood flow and maternal heart rate and increased maternal mean arterial blood pressure at a dose 1-fold and 0.25-fold the recommended maximal ocular dose at 2.5% and 10%, respectively. In the fetus, it produced acidosis and hypoxemia.

Phenylephrine hydrochloride was not mutagenic in bacteria (*Salmonella typhimurium* strains) with or without metabolic activation. At nearly toxic doses, the evidence for mutagenicity was equivocal in the mouse lymphoma L5178Y/TK+/- assay in incubations without metabolic activation. Phenylephrine induced sister chromatid exchanges in CHO cells.

Except for the findings of decreased fetal body weight and the onset of early labor in rabbits, and maternal hypertension and reduced uterine blood flow and subsequent oxygen delivery to the fetus in the sheep, the data support low potential for similar systemic adverse effects to be observed in humans following treatment with up to 3 drops of phenylephrine 2.5% or 10%. It must be considered that the actual safety margins are expected to be higher, as the intended dosing in humans is for only a single day and 100% systemic absorption after ocular administration is not expected. The effects on the fetus, labor, blood pressure, and uterine blood flow are included in the label.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The recommended changes to Sections 8.1, 13.1 and 13.2 of the proposed label are as follows:

Note: Strikethrough represents deleted text, and italicized font represents inserted text.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category C: Animal reproduction studies have (b) (4)

(gestation day 22 until delivery). Assuming 100% absorption after ocular administration,

this dose is approximately 4-fold and 1-fold the recommended maximal ocular dose at 2.5% and 10%, respectively, based on body surface area. Additionally, phenylephrine (0.12 mg/kg/day) administered intravenously to sheep once every 3 days (for 8 cycles) during the third trimester was shown to induce maternal hypertension and reduce uterine blood flow and subsequent oxygen delivery to the fetus. This dose is 1-fold and 0.25-fold the recommended maximal ocular dose at 2.5% and 10%, respectively, based on body surface area.

It is not known whether phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% should be given to a pregnant woman only if clearly needed.

(b) (4)



2 Drug Information

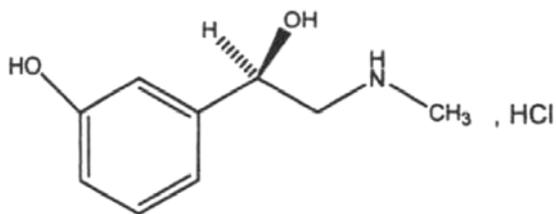
2.1 Drug

Generic Name: Phenylephrine Hydrochloride

Chemical Name: (*R*)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol

Molecular Formula/Molecular Weight: C₉H₁₃NO₂•HCl /203.67 g/mol

Structure:



Pharmacologic Class: α₁-adrenergic receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

None

2.3 Drug Formulation

Component	2.5% Formulation Quantity (%w/v)	10% Formulation Quantity (%w/v)	Function
Phenylephrine HCl	2.5%	10%	Active Ingredient
Sodium Phosphate Monobasic, (b) (4)	(b) (4)		
Sodium Phosphate Dibasic, (b) (4)			
Boric Acid			
Benzalkonium Chloride	0.01%	0.01%	Antimicrobial preservative
Sodium Hydroxide	As needed	As needed	pH adjustment
Hydrochloric Acid	As needed	As needed	pH adjustment
Water for Injection	Q.S.	Q.S.	(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% is indicated to dilate the pupil (b) (4). For adults, the dosing recommendations are to apply one drop of either 2.5% phenylephrine or 10% phenylephrine every 3-5 minutes to each eye as required, up to a maximum of 3 drops.

Regarding the use in children and the elderly, the proposed label includes the following language: (b) (4)

2.7 Regulatory Background

Due to its long and established use, phenylephrine hydrochloride has a status of GRASE and an OTC monograph was developed for use as an ophthalmic vasoconstrictor for relief of ocular redness at concentrations between 0.08% and 0.2%. Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, are currently being marketed in the US for use as mydriatics. However, these products are outside the concentrations approved in the OTC monograph. Seeking to market an FDA approved product, the sponsor submitted this NDA as a 505(b)(2) application on 10/19/2011. A Refuse to File letter was issued on 12/16/11 due to CMC deficiencies. The sponsor

resubmitted the NDA on 9/21/2012. The application was granted priority review classification on the filing letter issued on 12/3/12.

3 Studies Submitted

3.1 Studies Reviewed

The NDA includes no reference to any nonclinical studies conducted by the ocular route. The sponsor is relying on the more than 70 years of clinical experience as a mydriatic to support the ocular safety of phenylephrine HCl. The nonclinical safety assessment of phenylephrine HCl after systemic administration relied on reports obtained from the literature. Particularly, the sponsor cited the toxicology package conducted by the National Toxicology Program (NTP) which includes general toxicology (14 day and 12-week repeated-dose studies), genetic toxicology, and carcinogenicity evaluation¹. The NTP publication contains references for reproductive toxicology evaluation. The NDA also includes a publication that showed that the ocular distribution of phenylephrine was limited by the corneal epithelium.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

This NDA is being submitted as a 505(b)2 application. The applicant relies on the Agency's findings of safety and effectiveness of the approved products under NDAs 084-300, 007-953, and 22-565 for additional information on the non-clinical safety for phenylephrine hydrochloride not included in this application.

- NDA 08-4300 – Cyclomydril (Approved Sept 1975; prescription) – Cyclopentolate HCl 0.2%; phenylephrine HCl 1% Ophthalmic Solution
- NDA 00-7953 – Prefrin-A (Approved July 1966; discontinued) – Phenylephrine HCl 0.12%;pyrilamine maleate 0.1% Ophthalmic Solution
- NDA 22-565 – Advil Congestion Relief (Approved May 2010; OTC) – Ibuprofen 200 mg;phenylephrine HCl 10 mg oral tablets

The concentration of phenylephrine HCl (0.12% or 1%) in these NDAs is lower than that intended in the current NDA and as such the studies will not support ocular concentrations of 2.5% and 10%. NDA 22-565 made a cross-reference to nonclinical data submitted under NDA (b) (4)

(b) (4) No nonclinical studies with phenylephrine HCl were reviewed under NDA (b) (4). As these are OTC products, there is no nonclinical information in the labels.

¹NTP Technical Report 322 on the Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride in F344/N Rats and B6C3F₁ Mice, NIH Publication No. 87-2578, January 1987

4 Pharmacology

Phenylephrine hydrochloride is an α -adrenergic receptor agonist. In the eye, phenylephrine acts locally to constrict ophthalmic blood vessels and the radial muscle of the iris. The constriction of the radial muscle (dilator pupillae) causes the pupil to dilate. After ocular instillation of 10% solution, maximal mydriasis is obtained in 60 to 90 minutes². Recovery from mydriasis occurs in about six hours. Phenylephrine causes constriction of most vascular beds, which is the basis for its decongestant action. It reduces renal, splanchnic, cutaneous and limb blood flow, and increases coronary blood flow. Other well known pharmacological effects include increased systolic and diastolic blood pressure after intravenous, subcutaneous or oral administration, and decreased intestinal motility.

Systemic side effects, related to the pharmacological activity, have been reported following topical administration of 10% phenylephrine hydrochloride^{3, 4}. These include elevated blood pressure, ventricular arrhythmia, myocardial infarction and subarachnoid hemorrhage. Because phenylephrine 10% eye drops can have powerful systemic effects, they should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis³.

The applicant submitted a publication by Edelhauser et al⁵ in which the effects of phenylephrine hydrochloride were investigated in albino rabbits with intact or denuded corneas. Phenylephrine hydrochloride 2.5% or 10% was instilled one drop every 5 minutes for a total of 3 drops. Phenylephrine caused a dramatic increase in corneal thickness and cellular vacuolation within the keratocytes and endothelial cells in denuded corneas but not in those with intact corneal epithelium. Epithelial damage to the outer surface was observed in corneas with intact epithelium (sloughing of the superficial, plate-like, squamous epithelial cell layers, cytoplasmic vacuoles in the basal epithelial cell layer and keratocytes located in the anterior stroma). The authors did not rule out the possibility that the epithelial damage in intact corneas was caused by the preservative benzalkonium chloride. In humans, corneal clouding has been observed following use of 10% phenylephrine hydrochloride when the corneal epithelium has been denuded or damaged³.

² Meyer SM and Fraunfelder FT, Phenylephrine Hydrochloride, *Ophthalmology* **87(11)**: 1177-1180 (1980)

³ Martindale Index, Micromedex® 2.0

⁴ Antoine ME et al., Pharmacokinetics of Topical Phenylephrine HCl, *Invest Ophthalmol Vis Sci* **25**:48-54, 1984

⁵ Edelhauser HF et al., The Effect of Phenylephrine in the Cornea, *Arch Ophthalmol* **97**: 937-947 (1979)

5 Pharmacokinetics/ADME/Toxicokinetics

The applicant presented the PK/ADME literature review summarized in the NTP report. The NTP literature review includes the following information:

- Phenylephrine hydrochloride is absorbed after oral administration, and the drug is rapidly absorbed following inhalation of nasal sprays or topical instillation into the eye
- Unlike epinephrine and norepinephrine, phenylephrine does not appear to bind appreciably to albumin, and the generally short duration of action (20 minutes) following intravenous injection suggests a rather rapid distribution, metabolism, and elimination.
- In humans, approximately 60% of an inhaled or orally ingested dose of phenylephrine appears in the urine within 24 hours as unchanged or conjugated phenylephrine, 30%-35% of the dose appears as meta-hydroxymandelic acid or its conjugates, and 8%-9% appears as meta-hydroxyphenylglycol or its sulfate or glucuronide conjugates.
- Monoamine oxidase is important in the metabolic conversion of phenylephrine. However, the termination of pharmacologic action is due to a decrease in concentration at the receptor site. It is not clear whether phenylephrine is also taken up by the presynaptic nerve terminal.

In addition, the applicant submitted a publication by Antoine⁴. In this publication, the rate of corneal penetration and the efflux of phenylephrine and its metabolites were evaluated in rabbit eyes. *In vitro*, using isolated rabbit corneas, the penetration rate of ¹⁴C-phenylephrine and its metabolites was increased about 9-fold in corneas where the epithelia was removed compared to corneas with intact epithelia. The rate constant for corneal penetration was $1.06 \times 10^{-3} \text{ hr}^{-1}$ when the epithelium is present and $1.25 \times 10^{-2} \text{ hr}^{-1}$ when the epithelium is denuded. Epithelial removal reduced the half-life for corneal efflux of phenylephrine from 24 minutes to 6 minutes. *In vivo*, ocular absorption of topically applied 0.1% phenylephrine was increased when the corneal epithelium was removed prior to application. Corneal concentrations of phenylephrine increased 3-fold, aqueous humor concentrations increased 10 to 17-fold and iris/ciliary body concentrations increased 6-fold upon epithelial removal. These studies indicate that the corneal epithelium is a barrier to the penetration and flux of phenylephrine, both in and out of the cornea. These studies also showed that the removal of the corneal epithelium greatly reduced the ocular metabolism of phenylephrine.

6 General Toxicology

No nonclinical studies by the ocular route were cited. The sponsor is relying on the more than 70 years of clinical experience as a mydriatic to support the ocular safety

of phenylephrine hydrochloride. Regarding systemic safety, 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%)⁶. 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 2.85 to 3.80-fold the highest proposed clinical dose, assuming 100% absorption after ocular administration (3 drops/eye at 10% and a 35 µL drop = 21 mg or 0.35 mg/kg). This safety margins are expected to be higher considering that the whole dose is not expected to be systemically absorbed. Therefore, the existent marketing experience provides support for the systemic safety of the intended clinical ocular doses.

The sponsor submitted the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride. This report is based on data collected from 12-week studies that began in December 1979 and on the 2-year studies that began in September 1980. General toxicology studies of 2-week and 12-week duration were conducted in rats and mice. Because the extensive clinical experience provides support for the safety of the proposed ocular doses, only the information pertinent to the label will be reviewed.

7 Genetic Toxicology

In the NTP studies, phenylephrine hydrochloride was not mutagenic in four tester strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, and TA98) in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 fraction. The experiment was performed twice, each in triplicate. The concentrations ranged from 0-10,000 µg/plate. The NTP report states that because the results were similar, data from only one experiment was shown. The mean ± standard error data were presented in the report.

The results of mutagenicity studies of phenylephrine hydrochloride were equivocal in the mouse lymphoma L5178Y/TK^{+/-} assay. A positive response was noted in the first trial without metabolic activation at the high dose of 1,500 µg/mL (Table 1). The NTP report states that this dose was toxic to the cells as the relative total growth (RTG) was 12.2%. However, this value is above the RTG threshold used in this assay (≥10%) for a valid result. The NTP report states these results were not reproduced in a second trial (data not shown). Phenylephrine hydrochloride was not tested in the presence of S9 fraction in the mouse lymphoma assay.

⁶ Clinical Pharmacology Online Index (FDA Library)

Table 1: Mutagenicity of Phenylephrine Hydrochloride in L5178Y/TK+/- Mouse Lymphoma Cells in the Absence of S9 Fraction

Compound	Concentration (µg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10 ⁶ clonable cells)
Distilled water					
		84	100.7	118.0	28
		75	94.0	95.0	27
		101	73.0	89.0	46
		88	90.7	96.0	(b) 32 (33)
Methyl methanesulfonate					
	5	527	62.5	38.9	281
		627	72.0	42.4	290
		635	65.3	33.4	324 (298)
Phenylephrine hydrochloride					
	125	99	83.3	89.8	40
		74	82.7	92.2	30
		88	85.0	86.2	35 (35)
	250	85	68.5	68.3	41
		103	80.8	79.6	42
		99	77.2	82.7	43 (42)
	500	94	62.3	45.1	50
		64	49.7	50.3	43
		72	102.8	56.4	23 (39)
	750	108	80.5	44.8	45
		83	93.3	46.2	30
		92	96.7	42.6	32 (35)
	1,000	120	84.2	33.0	48
		121	62.0	19.9	65
		125	86.5	26.9	48 (54)
	1,500	151	62.2	13.0	81
		162	65.3	11.2	83
		149	70.5	12.3	70 (78)

(a) Experiments were performed twice, all doses were tested in duplicate or triplicate. Because the results from the two experiments were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5 /ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

(b) The mean of the results of replicate determinations is the number in parentheses.

The NTP report states that phenylephrine hydrochloride induced sister chromatid exchanges (SCEs) in the absence of metabolic activation in Chinese hamster ovary cells (CHO). Additional data was available in a publication by Anderson et al.⁷

The criteria for a positive response in this assay included either a statistically significant dose-related increase in the number of SCE or a statistically significant and

⁷ Anderson, BE et al., Chromosome Aberration and Sister Chromatid Exchange Test Results with 42 Chemicals, *Environ Molec Mutagen* 16(Suppl 18):55-137 (1990)

reproducible positive response at any one of the test concentrations. The increase in SCEs was statistically significant at ≥ 2000 $\mu\text{g/mL}$ in both experiments (Table 2A). At 1500 $\mu\text{g/mL}$, a statistically significant positive response was noted in one of the duplicate experiments. The NTP report concluded that there was no increase in SCE in the presence of S9 fraction (Table 2B). However, given the statistical analysis was not included in the publication and values at ≥ 9000 $\mu\text{g/mL}$ were similar to those observed in the positive assay without S9 fraction, it is difficult to make a definite assessment of the results in the presence of S9 fraction.

Phenylephrine hydrochloride did not cause an increase incidence of chromosomal aberrations in CHO cells at doses up to 2,500 $\mu\text{g/mL}$ (-S9 fraction) and 10,000 $\mu\text{g/mL}$ (+S9 fraction). The publication by Anderson et al states that doses $> 2,500$ $\mu\text{g/mL}$ (-S9 fractions) were toxic.

Table 2: Induction of Sister-Chromatid Exchanges in Chinese Hamster Ovary Cells by Phenylephrine Hydrochloride

(A) Obtained from Anderson et al.

PHENYLEPHRINE HCL

COPYRIGHT MATERIAL WITHHELD

PHENYLEPHRINE HCL

COPYRIGHT MATERIAL WITHHELD

(B) Obtained from the NTP Report

- S9 (b)		+ S9 (c)	
Dose (µg/ml)	SCE/Cell (d)	Dose (µg/ml)	SCE/Cell (d)
Medium	9.1	Medium	10.2
Phenylephrine hydrochloride		Phenylephrine hydrochloride	
1,500	12.1	8,500	10.6
2,000	11.4	9,000	11.1
2,500	11.9	10,000	11.8
Mitomycin C		Cyclophosphamide	
0.001	15.3	0.400	13.5
0.010	48.8	2.000	27.0

(a) SCE = sister-chromatid exchange

(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 2 hours at 37° C; 2 hours after initiation of treatment, 10 µM BrdU was added, and incubation was continued for an additional 22-24 hours. (Due to chemically induced cell cycle delay, cells treated with study compound were allowed to incubate an additional 6 hours to accumulate sufficient metaphases for analysis.) Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).

(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

(d) Cells were collected by mitotic shake-off, tested for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air dried (Galloway et al., 1985).

In summary, according to the data presented in the NTP report, phenylephrine hydrochloride was not mutagenic in bacteria (*Salmonella typhimurium* strains) with or without metabolic activation. At nearly toxic doses, the evidence for mutagenicity was equivocal in the mouse lymphoma L5178Y/TK^{+/−} assay in incubations without metabolic activation. Phenylephrine induced SCEs in CHO cells. All assays included negative and positive controls that showed the expected responses. The NTP report states that these studies were GLP-compliant.

The reviewer performed a literature search (Pubmed and Toxnet databases). A publication by Hilliard et al⁸ showed phenylephrine was negative in the chromosomal aberration assay (± S9 fraction) in CHO cells and caused little cytotoxicity at doses of 6, 8, and 10 mM (1222-2037 µg/mL). The authors indicated that these results confirm the negative aberration test in CHO cells published by Anderson et al⁷. Given the long history of clinical use, it is not expected that ocular use of phenylephrine at the intended dose regimen will create a mutagenic risk.

8 Carcinogenicity

In the NTP report, 2-yr carcinogenicity studies were conducted in rats and mice. Diets containing 0, 620 or 1250 ppm phenylephrine hydrochloride were fed to groups of 50 F344/N rats of each sex for 103 weeks. Diets containing 0, 1,250 or 2,500 ppm were

⁸ Hilliard CA et al. Chromosome Aberrations *In Vitro* Related to Cytotoxicity of Nonmutagenic Chemicals and Metabolic Poisons, *Environ Mol Mutagen* 31: 316-326 (1998)

fed to groups of 50 B6C3F₁ mice of each sex for 103 weeks. Rats were 6-7 week old and mice were 7-8 wks old at study initiation.

The doses were selected based on the results of the 12-week repeated-dose toxicology studies at phenylephrine hydrochloride doses of 0, 1,250, 2,500, 5,000, 10,000 and 20,000 ppm. In rats, mortalities were observed at $\geq 5,000$ ppm in males. In addition, final mean body weight gains were decreased in males at all doses (46-93%) and in females at $\geq 2,500$ ppm (30-87%) compared to the control groups. There were concomitant decreases in food consumption. In mice, mortalities were observed in males at $\geq 10,000$ ppm. Mean body weight gain was decreased at $\geq 5,000$ ppm in males (25-96%) and at all doses in females (21-79%). However, food consumption was slightly higher (1.2x) in high dose mice compared to controls. The NTP report states that if the feed consumption data are correct, the approximate lethal daily dose was 300 mg/kg for male rats and 1,400 mg/kg for male mice.

In rats, pupil size was generally smaller in all phenylephrine hydrochloride dosed groups compared to controls, although there was not a clear dose response. This finding is not consistent with the expected mechanism of action (dilation of the pupil), unless it was due to rebound miosis. Absolute adrenal and heart weights were lower (13-37%) than controls at 20,000 ppm. Increases in relative weights for both organs could be related to the lower body weight. The data for any other organs weighed was not shown. No histopathological correlate for the changes in adrenal and heart weights was reported. Chronic keratitis of the eye was observed in 4/8 males and 8/10 females at 20,000 ppm and 4/10 males and 6/10 females at 10,000 ppm (data not shown). Histopathological findings in rats included minimal to mild testicular atrophy in 4/8 males and seminal vesicle atrophy in 5/6 males at 20,000 ppm, and mild to moderate ovarian atrophy in 5/10 females at 20,000 ppm (data not shown).

In mice, inflammatory eye lesions (acute keratitis, panophthalmitis, or phthisis bulbi) were observed in 3/10 males and 2/10 females at 20,000 ppm (data not shown). Estimated food consumption was higher at 20,000 ppm (17% in males; 23% in females). The absolute and relative adrenal gland weights for mice at 20,000 ppm were greater (1.1-3X) than those of the controls. The absolute heart weight was decreased at 20,000 ppm (7% in females; 13% in males; statistically significant for males). The relative heart weight was increased for females at 20,000 ppm. This increase could be related to the lower body weight. No histopathological correlate was reported for the organ weight changes.

Results 2-yr carcinogenicity studies:

Rats: The mean body weights were 3-8% lower in the low dose and 4-15% lower in high dose males throughout the study compared to controls. High dose females had body weights 4-10% lower than controls throughout the study. Body weights of low dose females were similar to those of controls. The body weight changes did not follow a progression with time. By the end of study, the body weight values were similar to controls (only 2.5%, 5%, and 3% lower for low-dose males, high-dose males, and high-

dose females, respectively). The average daily feed consumption was similar for dosed and control male and female rats. The average amount of phenylephrine hydrochloride consumed per day was approximately 22 mg/kg and 47 mg/kg for low dose and high dose male rats, respectively; and 26 mg/kg and 54 mg/kg for low dose and high dose female rats, respectively.

The survival of the high dose group of male rats was significantly greater than that of the controls after Week 98 (Table 3).

Table 3: Survival of Rats in the Two-Year Carcinogenicity Study

	Control	620 ppm	1,250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	17	8
Killed at termination	30	33	41
Died during termination period	0	0	1
Survival P values (c)	0.019	0.694	0.021
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	8	16	14
Killed at termination	42	34	35
Died during termination period	0	0	1
Survival P values (c)	0.208	0.071	0.212

(a) Terminal-kill period: week 104

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

The report states (data not shown) that no phenylephrine hydrochloride specific clinical signs of toxicity or ophthalmologic findings were noted in any group of dosed rats.

No increases in the incidences of neoplastic lesions were clearly related to dosing with phenylephrine hydrochloride. In male rats, mononuclear cell leukemia and pheochromocytomas of the adrenal gland occurred with negative trends (the incidences in the low and high dose group were lower than those in the controls). Greater incidences were noted for the following non-neoplastic findings:

- Liver: Chronic focal inflammation was observed at increased incidences in dosed rats (male: 2/50, 13/50, and 17/50; female: 17/50; 28/50; 35/50 at the control, low dose, and high dose, respectively).

The NTP report states that the lesion did not differ in character from the lesion that occurs spontaneously in the F344 rat. It was characterized by the presence of mononuclear cells scattered around bile ducts in the portal triad regions of hepatic lobules.

- Lung: Perivascular cuffing of the lung was observed with increased incidences in dosed rats (male: control, 2/50; low dose, 12/50; high dose, 8/50; female: 4/50 control, 6/50 low dose, and 7/50 high dose)
- Prostate Gland: The incidence of inflammation was increased in dosed versus control male rats (control, 10/50; low dose, 24/50; high dose, 24/50).
The NTP report states that these lesions were similar to those that spontaneously arise in the F344 rat but were subjectively judged to be more severe in dosed rats than in control rats.

Dosing solution analysis showed all dietary concentrations were within 10% of target value.

Mice: The mean body weight of low dose male mice was 4%-10% lower than that of the controls throughout most of the study. The mean body weights of low dose and high dose female mice were approximately 4%-7% and 4%-10% lower than that of the controls after Week 25. The average daily feed consumption for the whole dosing period by low dose and high dose male mice was 93% and 88% that of the controls. In females, it was slightly higher (6%) in low and high dose female mice (Note: The NTP report states the average feed consumption was 94% and 93% that of the controls, respectively, which is not reflected by the data). Based on feed consumed, the estimated average amount of phenylephrine hydrochloride consumed per day was 132 mg/kg and 264 mg/kg for low dose and high dose male mice, respectively; and 135 mg/kg and 276 mg/kg for low dose and high dose female mice, respectively..

No significant differences in survival were observed between any groups of either sex (Table 4). However, similar to what observed in rats, there was a trend towards higher survival in high-dose males.

Table 4: Survival of Mice in the Two-Year Carcinogenicity Study

	Control	1,250 ppm	2,500 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	12	7
Accidentally killed	2	0	0
Killed at termination	35	38	43
Survival P values (c)	0.120	0.820	0.149
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	16	16
Killed at termination	37	34	34
Survival P values (c)	0.664	0.806	0.692

(a) Terminal-kill period: week 104

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

The NTP report states (data not shown) that no phenylephrine hydrochloride specific clinical signs of toxicity or ophthalmologic findings were noted in any group of dosed rats.

No neoplastic lesions were clearly related to dosing with phenylephrine hydrochloride. The following neoplastic findings showed an increase incidence in males and/or females. However, these findings showed no statistical significance and were not mentioned in the NTP report as having any relevance.

- Lung: Increased incidence of alveolar/bronchial adenoma (4/50, 6/50, and 9/50 in males and 1/50, 3/50, and 5/50 in females in control, low dose, and high dose groups, respectively).
- Liver: Increased incidence of hepatocellular carcinoma was noted in males (4/50, 7/50, and 9/50 in males); not observed in females at any dose.
- Integumentary System: Increased incidence of subcutaneous tissues fibrosarcoma was noted in males (0/50, 4/50, and 4/50). No increase was observed in females (1/50, 1/50, and 2/50).

The reviewer confirmed these findings were within the spontaneous incidence range reported by Haseman et al⁹; liver adenoma/carcinoma (10-68%), lung adenoma/carcinoma (4-32%), skin fibrosarcoma (0-24%). Therefore, as assessed by the NTP report authors, these findings were not considered toxicologically relevant.

No non-neoplastic lesions were clearly related to dosing with phenylephrine hydrochloride, although the incidence of focal cellular change in the liver was slightly

⁹ Haseman JK et al., Spontaneous Neoplasm Incidences in Fisher 344 and B6C3F1 Mice in Two-Year Carcinogenicity Studies: A Natinal Toxicology Program Update, *Toxicol Pathol* **266(3)**: 428-41 (1998).

increased. The NTP report considered the incidence was increased in high dose males (control, 0/50; low dose, 2/50; high dose, 7/50) but not increased in females (0/50; 2/50; 1/50). Given the low incidence and lack of a dose response, the reviewer believes it is difficult to attribute the finding to the test article in females.

Dosing solution analysis showed all dietary concentrations were within 10% of target value.

In conclusion, there was no evidence of carcinogenicity of phenylephrine hydrochloride in male or female rats given 620 or 1,250 ppm in the feed or in male or female mice given 1,250 or 2,500 ppm in the feed. Based on the feed consumed, the average daily doses (male and female combined) were estimated to be 24 mg/kg for low dose rats, 50 mg/kg for high dose rats, 133 mg/kg for low dose mice, and 270 mg/kg for high dose mice. It should be taken into consideration that these estimated average daily doses may be overestimated as no correction for food spillage was made by the authors. Several 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,). Assuming 100% absorption after ocular administration, the 2.5% and 10% doses when given at the 3 drops/eye maximal dose are equivalent to 0.0875 mg/kg and 0.350 mg/kg, respectively (based on a 35 µL drop volume and 60 kg body weight). Based on body surface area, the human equivalent doses of LOAELs for non neoplastic lesions are 3.89 mg/kg (24 mg/kg low dose in rats) and 21.9 mg/kg (270 mg/kg high dose in mice). Therefore, the non-neoplastic findings were observed at 44-fold and 11-fold (rats) and 249-fold and 63-fold (mice), respectively, the recommended maximal ocular dose at 2.5% and 10%.

9 Reproductive and Developmental Toxicology

The NTP report provides the following summary: “Phenylephrine given to pregnant rabbits during the last third of gestation produced fetal growth retardation and the onset of early labor (Shabanah, 1969). The use of medications containing phenylephrine during the first 4 months of pregnancy was associated with a greater than expected number of eye, ear, and other minor malformations in humans (Heinonen, 1977). Two other epidemiologic studies found no association between congenital disorders and use of phenylephrine during pregnancy (Jick, 1981; Colley, 1982). Para-sympathomimetic agents consistently caused external and cardiac malformations when administered to chick embryos, but phenylephrine did not cause similar defects (Hodach, 1975; Bruyere, 1983).”

In the study from Shabanah et al¹⁰, the effects of phenylephrine on fetal growth and the onset of labor were studied during the 2nd half of pregnancy in NZW rabbits (~3

¹⁰ Shabanah MD et al, Effect of Epinephrine on Fetal Growth and the Length of Gestation, *Surg. Gynecol. Obstet.* **129(2)**: 341-343 (1969)

kg). According to the authors, the rabbit uterus is similar to that of humans in its response to epinephrine at this stage of pregnancy. The author's main objective was to determine the effects phenylephrine-induced vasoconstriction on the rabbit fetal growth during the late 2nd or 3rd trimester of gestation and on delivery. The following 3 dose regimens were used:

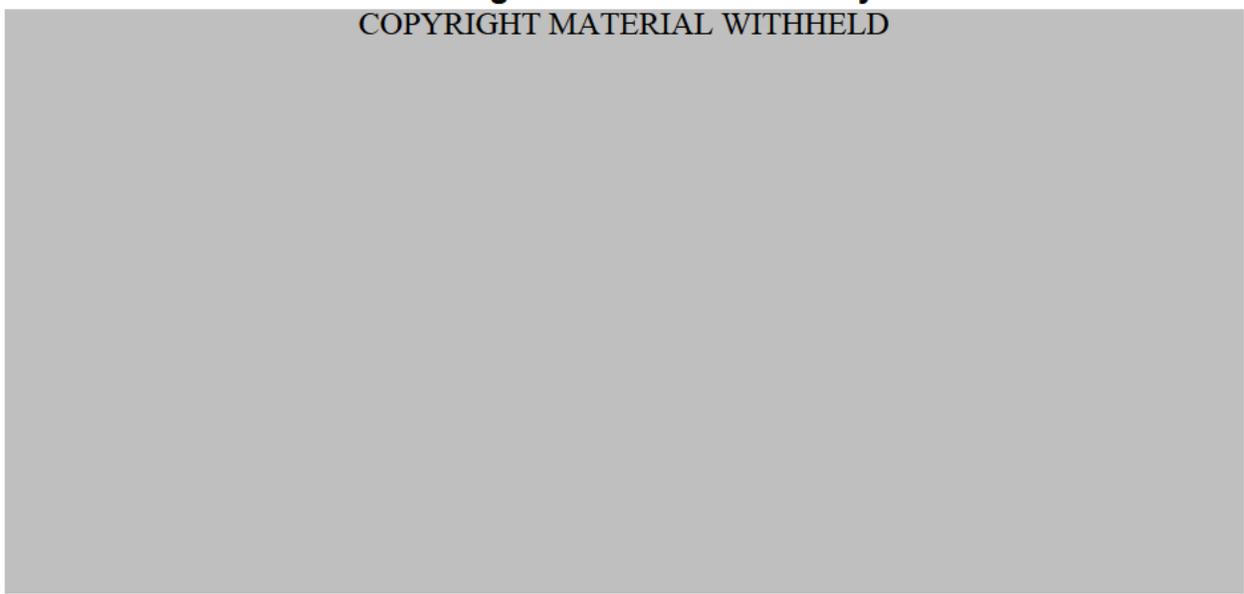
- Group 1: 7 rabbits were injected SC with 1 mg of phenylephrine hydrochloride in 1 mL of normal saline solution, 3x/day from GD22 until delivery; 3 rabbits served as controls.
- Group 2: 5 rabbits were injected SC with 1 mg of phenylephrine hydrochloride in 1 mL of normal saline solution, 3x/day from GD22 until delivery; 5 rabbits served as controls (the only apparent difference between Groups 1 and 2 is that the animals were mated on different dates).
- Group 3: 2 rabbits were treated with phenylephrine hydrochloride from GD16 (midpregnancy), "on" (although not stated, treatment is presumed to have extended through delivery).

The controls of all groups were not injected with saline solution because, according to the authors, this had previously given negative results. The placentae of 2 rabbits in Group 3 were sectioned for histologic study of the placental vessels; the placental weights were also recorded. Urine samples of the 2 rabbits in Group 3 and of 2 of the controls in each of Groups 1 and 2 were tested for glucose levels with Clinitest[®] tablets, 3x/day as of the 4th day of treatment.

Results: A number of rabbits in all phenylephrine treated groups gave birth to litters of low birth weight, some being premature and others full term (Table 5; copied from Shabanah et al¹⁰).

Table 5: Litter Data - Birth Weight and Onset of Delivery

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The authors stated that it is difficult to explain the cause of the high birth weight of the litter born to rabbit 2, Group 3. They suggested this may be due in part to hyperglycemia as this rabbit showed high blood glucose levels, in contrast to rabbit 1 of the same group which had normal glucose levels. No major changes in the vessel walls were seen in the 2 rabbits examined.

Although the study does not completely fulfill regulatory requirements, it shows phenylephrine hydrochloride caused a decrease in fetal weight and onset of labor, under the conditions of the study. Therefore, the reviewer finds it acceptable to use this data in the label to provide appropriate risk awareness. A dose of 1 mg 3x/day (3 mg/3 kg or 1 mg/kg) is equivalent to a human dose of 0.325 mg/kg. This provides safety margins of at least 3.69-fold and 0.93-fold, respectively, for the 2.5% and 10% doses when given at the 3 drops/eye maximal dose (0.088 mg/kg and 0.350 mg/kg, respectively, assuming a 35 µL drop volume and 60 kg body weight). The actual safety margins are expected to be higher, as the intended dosing in humans is for only a single day and 100% systemic absorption after ocular administration is not expected.

This reviewer performed a literature search (Micromedex[®] 2.0 Reprotox Database) and found an additional study by Cottle et al¹¹ investigating the effects of phenylephrine on maternal and cardiovascular indices and blood oxygenation in the sheep. In this study, sheep were 1-4 yrs old and weighed 45-64 kg. Phenylephrine (4 µg/kg/min) was infused IV (30 min) by a cannula during the third trimester of pregnancy at a dose the authors stated was equivalent to the dose in one “cold” tablet. Each animal received 8 treatments at least 3 days apart with cardiovascular indices and blood oxygenation parameters evaluated after each treatment. Phenylephrine depressed uterine blood flow and maternal heart rate (both, ~40% below control) and increased maternal mean arterial blood pressure (50% above control). In the fetus, it produced acidosis and hypoxemia. Phenylephrine depressed fetal arterial blood PO₂ (30%) and blood pH, and increased PaCO₂ (12%), but had little effect on mean arterial blood pressure and heart rate.

The Micromedex 2.0 Index reports that phenylephrine and other alpha adrenergic agonist have the potential to induce maternal hypertension and to reduce uterine blood flow at doses comparable to those used to produce therapeutic effects. Uterine blood vessels contain only alpha adrenergic receptors, which are capable of causing constriction when stimulated. Normally, these vessels are dilated. The Index cites the study by Cottle et al above, where a dose of phenylephrine equivalent to the content of one cold tablet was shown to decrease uterine blood flow. However, as indicated in the paragraph from the NTP report (see above), the Index also states that an association with some congenital anomalies in humans has not been confirmed. Therefore, although there is a theoretical risk, it is unknown if phenylephrine increases the incidence of birth defects in humans.

¹¹ Cottle MKV et al, Effects of Phenylephrine and Sodium Salicylate on Maternal and Fetal Cardiovascular Indices in Blood Oxygenation in Sheep, *Am J Obstet Gynecol* **143**:170-176 (1982)

11 Integrated Summary and Safety Evaluation

This NDA is being submitted as a 505(b)2 application. No nonclinical studies were conducted. The NDA includes no reference to any publications of nonclinical studies conducted by the ocular route. The sponsor is relying on the more than 70 years of clinical experience as a mydriatic to support the ocular safety of phenylephrine hydrochloride.

Given the extensive clinical experience, the ocular effects of phenylephrine hydrochloride are well known. These include rebound miosis, precipitation of angle-closure glaucoma, changes in intraocular pressure, conjunctival vasoconstriction, irritation, ocular pain, corneal punctuate keratitis, corneal edema, transient pigment floaters, and corneal clouding when the corneal epithelium has been denuded or damaged. Ophthalmic solutions of phenylephrine are contraindicated in patients with angle-closure glaucoma.

Systemic side effects, related to the pharmacological activity, have been reported following topical administration of 10% phenylephrine hydrochloride. These include elevated blood pressure, ventricular arrhythmia, myocardial infarction and subarachnoid hemorrhage. Because phenylephrine 10% eye drops can have serious systemic effects, they should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis

In the current NDA, the sponsor relied on reports obtained from the literature to provide nonclinical safety support for systemically administered phenylephrine hydrochloride. Particularly, the applicant cited the toxicology package conducted by the National Toxicology Program (NTP) which includes general toxicology (14-day and 12-week repeated-dose studies), genetic toxicology, and carcinogenicity evaluations. The NTP publication also contained references for reproductive toxicology evaluation. In evaluating the clinical significance of these findings, it must be considered that the duration of the nonclinical studies (12 weeks or 2 years) was considerably longer than that of the intended clinical duration (1 day). Therefore, the safety margins are expected to be higher as the intended dosing in humans is 1-3 drops on a single day, and complete (100%) systemic absorption after ocular administration is not expected.

In 12-week repeated-dose studies, mortalities were observed in males at $\geq 5,000$ ppm in rats and at $\geq 10,000$ ppm in mice. Based on feed consumed, the estimated lethal daily dose was 300 mg/kg for male rats and 1,400 mg/kg for male mice (139-fold and 334-fold, respectively, the recommended maximal ocular doses based on body surface area). No mortalities were observed at doses that were ≤ 50 -fold the recommended maximal ocular doses (Table 6). It should be taken into consideration that the estimated average daily doses may be overestimated as no correction for food spillage was made by the authors.

Target tissues identified included the eyes in both species, the testes and seminal vesicles in male rats and the ovaries in female rats. The inflammatory eye

lesions were considered by the authors secondary to the pharmacologic drying action of phenylephrine, which reduces ocular secretions and thereby predisposes the cornea to irritation and inflammation. The inflammatory eye lesions were observed in mice and rats fed diets containing 20,000 ppm (~3,800 mg/kg based on feed consumed) and $\geq 10,000$ ppm (~675 mg/kg based on feed consumed) phenylephrine hydrochloride, respectively. Histopathological findings in rats included minimal to mild testicular atrophy and seminal vesicle atrophy in males and mild to moderate ovarian atrophy in females at 20,000 ppm (~1,500 mg/kg based on feed consumed). At the NOAEL, the safety margins for these findings are at least 555-fold and 139-fold, respectively, the recommended maximal ocular doses at 2.5% and 10%, based on body surface area (Table 6).

Phenylephrine hydrochloride showed no evidence of carcinogenicity in male or female rats given 620 or 1,250 ppm or in male or female mice given 1,250 or 2,500 ppm in the feed for 2 years. Based on the feed consumed, the average daily doses (male and female combined) were estimated to be 24 mg/kg for low dose rats, 50 mg/kg for high dose rats, 133 mg/kg for low dose mice, and 270 mg/kg for high dose mice. In male rats, mononuclear cell leukemia and pheochromocytomas of the adrenal gland occurred with negative trends; the incidences in the high dose group were lower than those in the controls.

Several non-neoplastic lesions were considered related to phenylephrine hydrochloride (chronic focal inflammation of the liver and perivascular cuffing in the lungs 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). Based on body surface area, the non-neoplastic findings in the rat (no NOAEL) were observed at 44-fold and 11-fold, the recommended maximal ocular dose at 2.5% and 10%, respectively (Table 6). The NOAEL in mice was 122-fold and 31-fold the recommended maximal ocular dose at 2.5% and 10%, respectively.

Phenylephrine given to pregnant rabbits during the last third of gestation produced a decrease in fetal weight and the onset of early labor at a dose of 1 mg 3x/day (3 mg/3 kg or 1 mg/kg). A dose of 1 mg/kg provides safety margins of at least 3.69-fold and 0.93-fold, respectively, the recommended maximal ocular dose at 2.5% and 10% (Table 6).

The Micromedex 2.0 Index reports that phenylephrine and other alpha adrenergic agonist have the potential to induce maternal hypertension and to reduce uterine blood flow at doses comparable to those used to produce therapeutic effects. Uterine blood vessels contain only alpha adrenergic receptors, which are capable of causing constriction when stimulated. Normally, these vessels are dilated. In the sheep, phenylephrine, at a dose equivalent to the dose in one "cold" tablet, depressed uterine blood flow and maternal heart rate and increased maternal mean arterial blood pressure. In the fetus, it produced acidosis and hypoxemia. An association with some congenital anomalies in humans has not been confirmed. Therefore, although there is a theoretical risk, it is unknown if phenylephrine increases the incidence of birth defects in humans.

The safety margins for the different adverse effects observed are shown in the table below:

Table 6: Toxicities Observed and Safety Margins Relative to the NOAEL

Toxicity	Species/study duration	NOAEL mg/kg	HED (normalized to BSA) mg/kg	Safety Margin 2.5% (0.0875 mg/kg) ^a	Safety Margin 10% (0.350 mg/kg) ^a
Mortalities	Rats (males); 12 weeks	115	18.6	213	53
	Mice (males); 12 weeks	470	38.2	437	109
Eye inflammation	Rats; 12 weeks	300	48.65	556	139
	Mice; 12 weeks	1440	117	1334	334
Testicular atrophy; seminal vesicle atrophy	Rats; 12 weeks	630	102.2	1168	291
Ovarian atrophy	Rats; 12 weeks	720	116.76	1334	334
Prostate inflammation	Rats; 2-yr carc	<22 ^b	<3.57	<41	<10
Chronic liver inflammation	Rats; 2-yr carc	<24 ^b	<3.89	<44	<11
Focal cellular change in the liver (males only)	Mice; 2-yr carc	132	10.7	122	31
Lungs perivascular cuffing	Rats; 2-yr carc	<22 ^b	<3.57	<41	<10
Decreased fetal weight; onset of early labor	Rabbits; GD ^c 22 until delivery	<1 ^b	<0.325	<3.69	<0.93
Decreased uteri blood flow and heart rate and increased mean arterial blood pressure in the mother; acidosis and hypoxemia in the fetus	Sheep; 8 treatments at least 3 days apart during 3 rd trimester	<0.120 ^b	<0.0884	<1	<0.25

^aHuman doses were calculated based on a maximum bilateral administration of 3 drops/eye, a 35 µL drop volume, and 60 kg body weight.

^bNo NOAEL was observed.

^cGD: Gestation day

According to the data presented in the NTP report, phenylephrine hydrochloride was not mutagenic in bacteria (*Salmonella typhimurium* strains) with or without metabolic activation. At nearly toxic doses, the evidence for mutagenicity was equivocal in the mouse lymphoma L5178Y/TK+/- assay in incubations without metabolic activation. Phenylephrine induced SCEs in CHO cells. Given the long history of clinical use, it is not expected that ocular use of phenylephrine at the intended dose regimen will create a mutagenic risk.

Therefore, except for the findings of decreased fetal body weight and the onset of early labor in rabbits, and maternal hypertension and reduced uterine blood flow and subsequent oxygen delivery to the fetus in the sheep, the data support low potential for similar systemic adverse effects to be observed in humans following treatment with up to 3 drops of phenylephrine 2.5% or 10%. It must be considered that the actual safety margins are expected to be higher, as the intended dosing in humans is for only a single day and 100% systemic absorption after ocular administration is not expected. The effects on the fetus, labor, blood pressure, and uterine blood flow are included in the label. Approval of the NDA is recommended.

CC list:

J. Milstein/PM
M. Nevitt/MO

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/s/

MARIA I RIVERA
02/20/2013

LORI E KOTCH
02/20/2013

Division of Transplant and Ophthalmology Products
Memorandum to the file for NDA 203510
Phenylephrine HCl Ophthalmic Solution 2.5% and 10%

Supporting Document/Submission Date/Type: 6/9-21-12/Resubmission (After refusal to file)

Date: October 16, 2012

From: María I. Rivera, PhD

To: Constantine Markos (PM)

Through: Lori E. Kotch, PhD

Re: NDA Fileability

This NDA was initially submitted on 10-21-11 and the Division refused to file due to lack of sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. The filing checklist was conducted by Aaron Ruhland, PhD (filed in DARRTS on 12-6-11) when the NDA was initially submitted. There are no nonclinical studies with this NDA; it is a 505(b)(2) application. It was fileable from the nonclinical point of view. However, the current reviewer has the following request to the sponsor:

In Module 4, provide copies of all nonclinical literature publications cited in the NDA. In the integrated summaries (Module 2), provide discussion regarding how the data contained within the cited publications supports the NDA based on the clinical dose regimen proposed. Published literature is viewed at the same level of scrutiny as original data, and expected to be of comparable/sufficient quality to support the NDA. The potential impact of study shortcomings (e.g. lack of GLP quality data, insufficient animal numbers or endpoint analyses, formulation differences, inadequate test article characterization, etc.) should be discussed in Module 2.

Cc list:

C. Markos/PM

M. Levitt/MO

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/s/

MARIA I RIVERA
11/02/2012

LORI E KOTCH
11/02/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-510 Applicant: Paragon Biotech Inc. Stamp Date: 10-21-2011

Drug Name: Phenylephrine HCl NDA/BLA Type: 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	✓		Electronic 505(b)(2) application which contains cited references under Section 4: Nonclinical Study Reports. Application in eCTD format accessible via Global Submit Review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	✓		Cross-reference is made to NDA 022-565, NDA 084-300, and NDA 007-953. NDA 084-300 was not found in DARRTS. NDA 022-565 (Advil Cold and Sinus PE) was a 505(b)(2) application and the pharm/tox review cross-references NDA (b) (4) for relevant information and data.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	✓		A single lot of USP-grade phenylephrine HCl from (b) (4) was used in the NTP studies. This was incorporated into the rodent chow.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	✓		Most are systemic Three published references are provided which describe toxicological findings following ocular administration.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		✓	505(b)(2) application; most studies are published references
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓		None requested.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		✓	Labeling to be determined.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	✓		
11	Has the applicant addressed any abuse potential issues in the submission?		✓	Phenylephrine can not be used in the manufacture of (b) (4)
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		✓	

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE? ✓**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

AARON M RUHLAND
12/05/2011

WILLIAM H TAYLOR
12/06/2011