CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208552Orig1s000

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

Application number:	208552
Supporting document/s:	1
Applicant's letter date:	March 23, 2016
CDER stamp date:	March 23, 2016
Product:	RHOFADE™ (oxymetazoline hydrochloride) Cream, 1.0%
Indication:	For treatment of persistent facial erythema associated with rosacea
Applicant:	Allergan, Inc.
Review Division:	Dermatologic and Dental Products
Reviewer:	Cindy Xinguang Li, Ph.D.
Supervisor/Team Leader:	Barbara Hill, Ph.D
Division Director:	Kendall Marcus, MD
Project Manager:	William Dawn

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This New Drug Application (NDA) is a 505(b)(1) application submitted by Allergan, Inc. for the marketing of RHOFADE™ [oxymetazoline hydrochloride (HCl)] topical cream, 1.0%. Oxymetazoline HCl is a synthetic, direct-acting, imidazoline-type α1A adrenoceptor agonist. Oxymetazoline HCl containing products have been sold as over-the-counter (OTC) products, including Afrin® (0.05%, nasal spray) and Visine L.R.® (0.025%, eye drops). The proposed product, 0.1% oxymetazoline HCl cream, is being developed for the treatment of persistent facial erythema associated with rosacea in adults aged 18 years or older. The proposed dosing regimen is once daily (q.d.) in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin.

1.2 Brief Discussion of Nonclinical Findings

The toxicity profile of oxymetazoline HCl topical cream has been well characterized by the nonclinical studies conducted by the sponsor. The overall nonclinical findings are summarized below:

- No evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay); and one in vivo genotoxicity test (mouse micronucleus assay at oral doses ≤ 2.5mg/kg/day).

- Repeat-dose dermal toxicity studies were conducted in rats for up to 6 months and in minipigs for up to 9 months with oxymetazoline cream. Tail lesions and local toxicities were observed in rats.

- The oral Tg.ras H2 mouse assay at doses up to 2.5 mg/kg/day oxymetazoline did not reveal any neoplastic changes. A treatment related increased incidence of non-neoplastic lesions was noted in kidney, brain and mesenteric lymph nodes.

- The potential fertility and early embryonic development study toxicity was evaluated after oral administration in rats. Decreased number of corpora lutea and increased post-implantation losses were noted at the high dose of 0.2 mg/kg/day; however, there were no effects on the fertility and mating parameters. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for rat early embryonic development was established at the high dose tested of 0.2 mg/kg/day.

- The potential embryo-fetal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 0.2 mg/kg/day. The C_{max} and $AUC_{0\text{-}tlast}$ at 0.2 mg/kg/day were 0.541 ng/mL and 3.43 ng.hr/mL on GD day 17, respectively.

- The potential embryo-fetal development toxicity was evaluated after oral administration in rabbits. The NOAEL for maternal toxicity was established at the mid-dose of 0.5 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 1.0 mg/kg/day. The C_{max} at 1.0 mg/kg/day was 14.0 ng/mL on GD day 17. The AUC_{0-24} at 1.0 mg/kg/day was 76.2 ng.hr/mL on GD day 17.

- The potential prenatal and postnatal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for prenatal and postnatal developmental effects was identified at 0.05 mg/kg/day based on increases in pup mortality at 0.2 mg/kg/day and decreased pup weights, observations at necropsy, and delayed sexual maturation at ≥0.1 mg/kg/day.

There are no significant safety concerns for oxymetazoline HCl cream at the proposed clinical dose. No nonclinical postmarketing requirement is recommended for this NDA.

1.3 Recommendations

1.3.1 Approvability

NDA 208552 for RHOFADE (oxymetazoline hydrochloride) Cream, 1.0% is approvable from a Pharmacology/Toxicology perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the RHOFADE label.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the RHOFADE label reproduced below. The pharmacologic class designation for oxymetazoline hydrochloride for the treatment of rosacea is alpha1A adrenoceptor agonist. A clean copy of the suggested wording for the nonclinical sections of the label is provided in Appendix 2.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

RHOFADE™ (b) (4) is an alpha1A adrenoceptor agonist indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

Reviewer's comments: The pharmacologic class for oxymetazoline is alpha1A adrenoceptor agonist.

8 USES IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on [redacted] RHOFADE™ [redacted] use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies *[(see Data)]*. In Aanimal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic expousures up to 3 times and 73 times, respectively, the maximum recommended human dose (MRHD) [*see Data*]. [redacted]

Animal Data

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis [redacted] Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogeneisis (3 times the MRHD on an AUC comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogeneisis (73 times the MRHD on an AUC comparison basis). Maternal toxicity was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of [redacted]

In a rat [redacted] perinatal and postnatal development study, oxymetazoline hydrochloride [redacted] was orally administered to pregnant rats once daily from gestation Dday 6 through lactation Dday 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (3 times the MRHD on an AUC comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights.

Delayed sexual maturation was noted at 0.1 and 0.2 mg/kg/day (2 times the MRHD and 3 times the MRHD on an AUC comparison basis, respectively). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (one-half of the MRHD on an AUC comparison basis). (b) (4)

[redacted]

8.2 Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breastmilk production, or to establish the level of oxymetazoline present in human breastmilk postdose. (b) (4)

[redacted] Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOFADE™ (b) (4) and any potential adverse effects on the breastfed child from RHOFADE™ (b) (4) or from the underlying maternal condition.

(b) (4)

[redacted]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymetazoline is (b) (4)

[redacted] ~~α~~alpha1A adrenoceptor agonist (b) (4)

[redacted] Oxymetazoline acts as a

(b) (4) vasoconstrictor- (b) (4)

12.3 Pharmacokinetics

Excretion

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Oxymetazoline hydrochloride was not associated with an increased incidence of neoplastic or proliferative changes in transgenic mice given oral doses of 0.5, 1.0, or 2.5 mg/kg/day oxymetazoline hydrochloride (b) (4) for 6 months. (b) (4)

(b) (4)

Oxymetazoline hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo gentoxicity test (mouse micronucleus assay). (b) (4)

(b) (4)

Effects on fertility and early embryonic development were evaluated in rats following oral administration of 0.05, 0.1, or 0.2 mg/kg/day oxymetazoline hydrochloride prior to and during mating and through early pregnancy. Decreased number of corpora lutea and increased post-implantation losses were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis). However, no treatment related effects on fertility or mating parameters were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis).

(b) (4)

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
2315-02-8

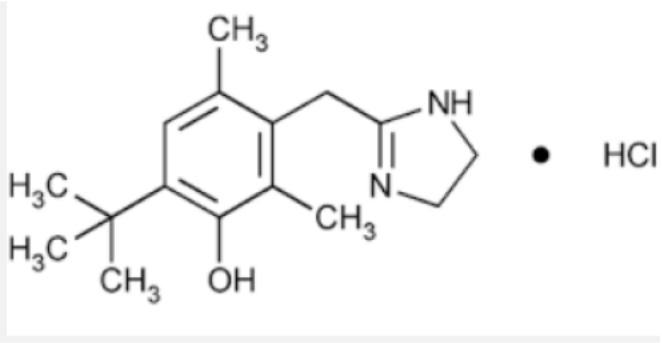
Generic Name
Oxymetazoline HCl

Code Name
R01AA05, R01AB07

Chemical Name
3-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethylphenol · hydrochloride

Molecular Formula/Molecular Weight
$C_{16}H_{24}N_2O \cdot HCl$ / 296.84

Structure or Biochemical Description



Pharmacologic Class
α1 adrenoceptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 107,983; NDA (b) (4); NDA 018471; NDA 019407; DMF# (b) (4)

2.3 Drug Formulation

The composition of Oxymetazoline HCl Cream, 1.0% is provided in the following table (copied from NDA submission).

Component	Function	Quality Standard	Concentration (% w/w)
Oxymetazoline HCl	Active	USP	1.0
Methylparaben	(b) (4)	NF	(b) (4)
Propylparaben		NF	
Phenoxyethanol		NF	
Sodium citrate dihydrate	(b) (4)	USP	
Citric acid anhydrous		USP	
Disodium edetate dihydrate		USP	
Butylated hydroxytoluene		NF	
Anhydrous lanolin		USP	
Medium chain triglycerides		NF	
Diisopropyl adipate		Non-compendial	
Oleyl alcohol		NF	
Polyethylene glycol 300		NF	
(b) (4) (PEG-6 stearate (and) Glycol stearate (and) PEG-32 stearate)		Non-compendial[a]	
Cetostearyl alcohol		NF	
(b) (4) (Ceteareth-6 (and) Stearyl alcohol)		Non-compendial	
(b) (4) (Ceteareth-25)		Non-compendial	
Purified water		USP	

[a] (b) (4) (b) (4) (PEG-6 stearate NF, glycol stearate NF, and PEG-32 stearate NF).

2.4 Comments on Novel Excipients

(b) (4) No safety issues have been identified on the excipients during this NDA review.

(b) (4)

[redacted] No safety issues have been identified for these excipients during this NDA review.

2.5 Comments on Impurities/Degradants of Concern

Two oxymetazoline degradants, [redacted] have been detected during storage at less than [redacted]%. A limit of [redacted]% for each degradant and [redacted]% for the combined total amount of the two degradants relative to drug substance are being proposed for the **release** specifications of the commercial cream formulation. A limit of [redacted]% for each degradant and [redacted]% for the combined total amount of the two degradants relative to drug substance are being proposed for the **shelf-life** specifications.

For the daily dose of the drug substance, the pharmacokinetics of oxymetazoline was evaluated following topical administration of RHOFADE in a thin layer to cover the entire face of adult patients and the median weight of cream for each dose administration was [redacted] g. The weight of drug substance is [redacted]mg as [redacted] of [redacted] g drug product. The ICH qualification threshold is 1% or 50ug Total Daily Intake, whichever is lower, for daily dose of less than 10 mg drug substance.

The proposed shelf-life specifications for [redacted] and [redacted] exceeded the ICH qualification threshold. The below nonclinical studies have been conducted to qualify the two impurities.

(1).Validation of an Analytical Method Using HPLC

The purpose of the study was to validate analytical methods for the quantification of [redacted] and [redacted] in DMSO. All acceptance criteria were met and the analytical methods for the determination of [redacted] and [redacted] were validated. The validated methods had been employed to determine the concentration of dosing formulations in nonclinical studies.

(2) [redacted] Bacterial Reverse Mutation Assay

[redacted] was evaluated for its mutagenic potential in the vitro bacterial reverse mutation assay. Four bacterial strains of Salmonella typhimurium (TA1535, TA1537, TA98, TA100) and one Escherichia coli strain (WP2) were used. The dose levels tested were 33.3, 100, 333, 1000, 3333 and 5000 µg/plate. Cytotoxicity was observed at ≥3333 µg/plate with TA100 and TA1535 strains in the presence and absence of S9 activation. [redacted] did not show any evidence of genotoxic activity under the study conditions tested.

(3) [redacted]: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)

[redacted] was tested for its potential to induce micronuclei in human peripheral blood lymphocytes (HPBL) in the absence and presence of an exogenous metabolic activation system. Cytotoxicity was observed at doses $\geq$ 225 µg/mL in the non-activated 24-hour exposure group. The doses therefore selected for microscopic evaluation were 50, 150, and 225 µg/mL for the non-activated 24-hour exposure group and 100, 200, and 315 µg/mL for the non-activated and S9-activated 4-hour exposure groups. No significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9. The results indicate [redacted] was negative for the induction of micronuclei under the study condition tested.

(4) [redacted]: Bacterial Reverse Mutation Assay

[redacted] was evaluated for its mutagenic potential in the vitro bacterial reverse mutation assay. Four bacterial strains of Salmonella typhimurium (TA1535, TA1537, TA98, TA100) and one Escherichia coli strain (WP2) were used. The dose levels tested were 3.33, 10.0, 33.3, 100, 333, 1000 and 3333 µg per plate for TA98 (in the presence and absence of S9 activation) and TA1537 and WP2 uvrA (in the presence of S9 activation). The dose levels tested were 3.33, 10.0, 33.3, 100, 333 and 1000 µg per plate for TA1535 (in the presence of S9 activation) and TA1537 and WP2 uvrA (in the absence of S9 activation). The dose levels tested were 0.33, 1.00, 3.33, 10.0, 33.3, 100 and 333 µg per plate for TA100 (in the presence and absence of S9 activation) and TA1535 (in the absence of S9 activation). Precipitate was observed at 3333 µg per plate with a few conditions. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. The results indicate [redacted] was negative for the ability to induce reverse mutations under the study conditions tested.

(5) [redacted]: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)

[redacted] was tested to evaluate the potential to induce micronuclei in HPBL in both the absence and presence of an exogenous metabolic activation system. Precipitate was observed at a dose of 500 µg/mL in each exposure group. Cytotoxicity was observed at doses ≥13 µg/mL in the non-activated 4-hour exposure group, at doses ≥ 16 µg/mL in the S9-activated 4-hour exposure group, and at doses ≥ 8 µg/mL in the non-activated 24-hour exposure group. The doses selected to be analyzed for evaluation were 4, 8, and 13 µg/mL in the non-activated 4-hour exposure group, 4, 8 and 16 µg/mL in the S9-activated 4-hour exposure group and 2, 5 and 8 µg/mL in the non-activated 24-hour exposure group. No significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9. The results indicate [redacted] was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system.

(6) Oxymetazoline Degradants: 13-Week Dermal and Systemic Toxicity Study in Minipigs

The objective of this study was to determine the potential dermal toxicity and systemic exposure of the two oxymetazoline degradants (b) (4) when administered dermally to groups of 4 minipigs per sex for a minimum of 13 weeks. 1% Oxymetazoline HCl (Oxy), (b) (4) (Oxy-Deg1 or Oxy-Deg-Low), or (b) (4) (Oxy-Deg2 or Oxy-Deg-High) were administered dermally to minipigs once a day. Dose administration was performed initially at a dose volume of 1.8 mL/kg over 10% of the body surface area (BSA) for up to 11 (females) or 14 days (males), resulting in doses of 0 (untreated), 18 (Oxy), 18/0.27 (Oxy-Deg-Low), or 18/0.54 (Oxy-Deg-High) mg/kg/day. These doses were not tolerated due to decreased gastrointestinal (GI) motility (manifested as abdominal distension and decreased fecal output). Therefore the animals were placed on a dosing holiday for 23-24 days. Dosing resumed at a dose volume of 0.4 mL/kg over 5% BSA for an additional 91 days, resulting in doses of 0 (untreated), 4 (Oxy), 4/0.06 (Oxy-Deg-Low), or 4/0.12 (Oxy-Deg-High) mg/kg/day.

Administration of oxymetazoline HCl at a dose level of 18 mg/kg/day either alone or in combination with degradants resulted in significant systemic toxicity and local dermal irritation similarly in all three treatment groups following 11 or 14 days of dose administration. Following a 23-24 day dosing holiday, dosing resumed at a reduced oxymetazoline HCl dose level of 4 mg/kg/day. Expected transient local dermal irritation was noted shortly following dosing re-initiation, but decreased in severity to non-adverse levels within approximately 2 weeks.

No adverse systemic findings were noted following dermal administration of Oxy, Oxy-Deg-Low, or Oxy-Deg-High at 4 (Oxy), 4/0.06 (Oxy-Deg-Low), or 4/0.12 (Oxy-Deg-High) mg/kg/day to minipigs for a minimum of 13 weeks. No significant differences were noted in in-life dermal toxicities among the Oxy, Oxy-Deg-Low, or Oxy-Deg-High dose groups, indicating no additional effect from the presence of the degradants. Based on microscopic evaluation, there was a marginally higher incidence of minimal diffuse epidermal hyperplasia in both Oxy or Oxy-Deg-High groups. Epidermal hyperplasia was also observed in the untreated skin area of two animals (one Oxy-Deg-High female and one Oxy male). This finding could be indicative of local irritation. There was no increase in incidence when the degradant was added to the oxymetazoline formulation, indicating no additional effect of the degradant. Noteworthy test article-related microscopic findings are summarized in the following table adapted from the submission.

Text Table 19
Summary of Noteworthy Microscopic Findings – Terminal Euthanasia (Day 129/127)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0/0**	**4/0**	**4/0.06**	**4/0.12**	**0/0**	**4/0**	**4/0.06**	**4/0.12**
No. Animals Examined	**4**	**4**	**4**	**4**	**4**	**4**	**3**	**4**
Skin, Administration site[b] (No. Examined)	4	4	4	4	4	4	3	4
Hyperplasia; epidermal	(0)[a]	(3)	(0)	(2)	(0)	(0)	(0)	(1)
Minimal	0	3	0	2	0	0	0	1

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Four sections were examined histologically from the administration sites of all animals. Only one entry was made per animal per observation (even if noted on all four sections examined) in Text Table 4 and the corresponding severity indicated represents the maximum severity noted among all four sections examined.

Overall, the nonclinical studies conducted indicate that the two degradants are non-mutagenic and the presence of up to (b)(4)% relative to drug substance does not significantly change the dermal or sy emic toxicity profile of the active drug substance. There are no safety issues identified for the impurities during this NDA review.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication is for treatment of persistent facial erythema associated with rosacea in adults aged 18 years or older. The proposed dosage and administration is once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin.

2.7 Regulatory Background

Oxymetazoline originally developed by E. Merck in Germany in 1961, was approved by FDA in 1964 as a nasal decongestant Drixine®. The drug is also the active ingredient in several over-the-counter drug products to treat allergic rhinitis and conjunctivitis (e.g. Afrin® nasal spray 0.05%, Dristan, Nasivin, Logicin, Vicks Sinex, and Visine L.R. and OcuClear® ophthalmic solution 0.025%).

Vicept Therapeutics, Inc. was the previous sponsor that submitted the IND. The sponsor was changed from Vicept to Allergan, Inc. during IND development. Several meetings were conducted with the sponsor during the clinical development.

3 Studies Submitted

3.1 Studies Reviewed

In addition to the studies reviewed under the present NDA submission, all other studies were reviewed under IND 107983.

Primary Pharmacology

1) Alpha-Adrenergic Activity of Oxymetazoline in a Functional In Vitro Cell-based Assay

Secondary Pharmacology

No studies were conducted

Safety Pharmacology

1) Effect of Oxymetazoline Hydrochloride on hERG Tail Current Recorded from Stably Transfected HEK293 Cells
2) Effects of Oxymetazoline Topical Cream in the Irwin Test in Rats
3) Oxymetazoline Hydrochloride Topical Cream: A Cardiovascular Safety Pharmacology Study Using Radiotelemetry in Conscious Male Gottingen Minipigs
4) Measurement of Respiratory Parameters in Conscious Rats by Whole Body Plethysmography Following Administration of Oxymetazoline Topical Cream

Pharmacokinetics

Table 1 Pharmacokinetics Program

Study Type	Study	Administration Method	GLP
Absorption	Single-dose PK in rats[a]	Intravenous	No
	Dermal and systemic PK in minipigs	Dermal	Yes
Distribution	Cross-species plasma protein binding	In vitro	No
	Melanin binding	In vitro	No
	Placental transfer in rats	Oral	No
	Systemic distribution/mass balance and topical distribution in rats	Intravenous and Dermal	No
Metabolism	Cross-species liver microsome metabolism	In vitro	No
	Dermal stability (human facial skin)	In vitro	No
	Cytochrome P450 inhibition in human liver microsomes	In vitro	No
	Cytochrome P450 induction in cultured human hepatocytes	In vitro	No
	Metabolite profiling and characterization in rats	Intravenous	No

GLP = good laboratory practice; PK = pharmacokinetic

[a] Also include distribution characterization.

Repeat dose toxicology

1) 7-Day Dermal (Semi-Occluded) Toxicity Study in the Rat with a 7 Day Treatment-Free Period
2) 28 Day Dermal (Semi-Occluded) Toxicity Study in the Rat with a 14 Day Treatment-Free Period
3) 13 Week Dermal (Semi-Occluded) Toxicity Study in the Rat
4) 26 Week Dermal (Semi-occluded) Toxicity Study in the Rat
5) A 28-Day Toxicity Study in Mini-pigs for the Evaluation of Oxymetazoline Topical Cream

6) 13 Week Dermal (Semi-Occluded) Toxicity Study in the Minipig with a 4 Week Treatment-Free Period
7) 39 Week Dermal (Semi-Occluded) Toxicity Study in the Minipig
8) Oxymetazoline HCl: 28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice
9) 13 Week Oral (Gavage) Toxicity Study in the Mouse

Genotoxicity

1) Bacterial Reverse Mutation Test
2) In Vitro Mammalian Cell Cytogenetic Test: Human Lymphocyte
3) Oral (Gavage) Mouse Micronucleus Test

Carcinogenicity

1) Oxymetazoline HCl: 26-week oral carcinogenicity study in Tg.rasH2 mice

Reproductive and Developmental Toxicology

1) Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation
2) Oral (Gavage) Developmental Toxicity Study in the Rat with Toxicokinetic Sampling
3) Oral (Gavage) Embryo-Fetal Development Study in the Rabbit
4) Oxymetazoline HCl: Oral Prenatal and Postnatal Developmental Study in Rats

Special Toxicology

1) Phototoxicity study in guinea pigs (Study No. TO9-5661)

Toxicology studies conducted with impurities

1) Oxymetazoline Degradants: 13-Week Dermal and Systemic Toxicity Study in Minipigs
2) (b) (4) (b) (4) Bacterial Reverse Mutation Assay
3) (b) (4) (b) (4) In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)
4) (b) (4) (b) (4) Bacterial Reverse Mutation Assay
5) (b) (4) (b) (4) In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)

3.2 Studies Not Reviewed

A 4-week dermal rat study was terminated early because non-occluded animals licked the application sites causing systemic adverse effects (peripheral vasoconstriction) characteristic of oxymetazoline.

The following studies were not reviewed because it was a preliminary study and longer term or pivotal studies have been reviewed.

1) Preliminary and 28 Day Dose Range Finding Study in the Mouse
2) Oral (Gavage) Fertility Dose Range Finding Study in the Rat
3) Oral (Gavage) Developmental Toxicity Dose Range Finding Study in the Rat
4) Oral (Gavage) Maximum Tolerated Dose (MTD) and 7 Day Dose Range Finding Study in the Rabbit
5) Oral (Gavage) Developmental Toxicity Dose Range Finding Study in the Rabbit
6) Oral (Gavage) Pre- and Post-Natal Development Dose Range Finding Study in the Rat

3.3 Previous Reviews Referenced

Pharmacology/Toxicology reviews under IND 107983.

4 Pharmacology

4.1 Primary Pharmacology

Oxymetazoline is an alpha1A adrenoreceptor agonist. Agonists in this category initiate their action by stimulating alpha1 adenoreceptors coupled to G proteins and phosphatase C, and in turn modulating their effects through a classic 7-transmembrane protein second messenger system. Alpha1 adenoreceptor agonists are vasoconstrictors, and thus have been used as decongestants to treat allergic rhinitis and conjunctivitis by decreasing erythema and edema of the nasal and ocular mucous membranes, respectively. This vasoconstriction property is being utilized for treatment of persistent facial erythema associated with rosacea in adults.

4.2 Secondary Pharmacology

In in vitro studies reported in the published literature, there are some indications of anti-inflammatory activities.

4.3 Safety Pharmacology

Neurological effects

Effects of oxymetazoline topical cream in the Irwin test in rats: The effects of oxymetazoline on behavior and on the central autonomic and somatic nervous systems were investigated in rats. Single topical doses of 0, 0.1, 0.25 or 0.5% oxymetazoline cream were administered to male Sprague-Dawley rats (6/group). Drug was detected in the plasma at all levels without exhibiting any dose-related trend. It did not affect awareness, motor activity and coordination, central excitation, reflexes, cardiovascular and respiratory systems, and autonomic profile.

Cardiovascular effects

The effects of oxymetazoline HCl on the cardiovascular system were evaluated in an in vitro HERG assay and in an in vivo cardiovascular safety pharmacology study conducted in minipigs.

Effect of oxymetazoline hydrochloride on hERG tail current recorded from stably transfected HEK293 cells: The drug inhibited hERG tail current in a dose-dependent fashion at concentrations of 30 μM and above ($p<0.001$ compared to vehicle). The estimated IC_{50} for current inhibition was 81 μM.

The validity of the assay was confirmed when E-4301 caused 94.3% inhibition of the current. The low-dose (10 μM) of oxymetazoline hydrochloride had no statistically significant inhibitory effect on the hERG tail current.

Oxymetazoline hydrochloride topical cream: A cardiovascular safety pharmacology study using radiotelemetry in conscious male Gottingen minipig: No drug effects on PQ, PR, QT, and RR intervals, heart rate, QtcF (Fridericia) interval, body temperature, mean systolic/diastolic/pulse arterial blood pressures, and physical activity were observed at concentrations up to 2.5% oxymetazoline HCl cream. At 6 hour, the plasma drug level in all four minipigs ranged between 0.394 to 2.59 ng/mL.

Pulmonary system

Measurement of respiratory parameters in conscious rats by whole body plethysmography following administration of oxymetazoline topical cream: No clinical changes were observed in respiration rate, tidal and minute volumes at concentrations up to 0.5% oxymetazoline HCl cream.

In the 4-week dermal study in minipigs conducted with oxymetazoline HCl cream (0.5- 2%), no changes in electrocardiographic parameters were observed at the topical dose level of 2% oxymetazoline HCl cream.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Systemic absorption of oxymetazoline was limited following repeated dermal application of oxymetazoline cream to rats (0.05% - 0.5%) and minipigs (0.25% - 2.5%). The bioavailability of dermally applied oxymetazoline ranged from 3.6% to 7.4% in rats. Plasma Cmax and AUC were generally dose-dependent in both rats and minipigs.

Following repeated dermal administration of oxymetazoline cream [0.5% - 1.5% once-a-day (QD) or twice-a-day (BID)] to minipigs for 7 days, oxymetazoline was absorbed into the skin, resulting in dermal concentrations in the μg/g range, with corresponding plasma concentrations in the pg/mL range. Unlike the plasma concentration–time profiles, the dermal concentration-time profiles of oxymetazoline following the repeated dermal applications were relatively flat over a 12-hour or 24-hour dermal dosing interval. Dermal accumulation of oxymetazoline was significant by Day 7, in contrast to little or no accumulation in the plasma after repeated dermal applications once per day. Steady-state dermal concentration levels were reached after 7 QD doses based on the comparison of Day 6 to Day 7 trough levels at 1% or 1.5% QD dose

levels. At steady-state, both dermal maximal concentrations (Cmax) and area under the concentration-time curve (AUC) following QD dosing increased with the increase in oxymetazoline doses.

Distribution

Oxymetazoline was absorbed into the circulation following oral administration to mice, rats, and rabbits, and was found to be extensively distributed in rats following IV bolus administration. However, no measurable concentrations (concentrations below limit of quantification, BLQ, <0.1 ng/mL) of oxymetazoline were detected in fetal plasma and amniotic fluid in rats following oral administration.

Metabolism

Binding of oxymetazoline to mouse, rat, minipig, and human plasma proteins, human serum albumin (HSA), and human alpha1-glycoprotein (AGP) was minimal to moderate in vitro. Literature shows that oxymetazoline undergoes biotransformation through the cytochrome P450 2C19 (CYP2C19) and uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) pathways. However, pharmacokinetic drug interactions between locally administered oxymetazoline and other systemically administered drugs are unlikely due to the low plasma concentrations of oxymetazoline anticipated following dermal administration and based on in vitro results that oxymetazoline had little or no inhibition and induction effect on various CYP subtypes.

Excretion

Oxymetazoline was eliminated with a half-life (T1/2) of 4.0 to 6.8 hours in rats following dermal application. The main route of elimination of oxymetazoline was via urinary excretion with ~60% of the dose, with oxymetazoline and metabolites representing ~20% and 40% of the dose, respectively.

Single intravenous dose pharmacokinetic study in rats (VEG0002)

Key study findings: In the single intravenous dose pharmacokinetic study (0.15 mg/kg), the maximum plasma drug level was achieved in 20 minutes, followed by rapid drug elimination. The volume of distribution and clearance rate was greater in males.

Table1. A summary of pharmacokinetic parameters following the intravenous dose of 15mg oxymetazoline hydrochloride/kg in rats.

Parameter	Males	Females
$C_{0\ (ng/mL)}$	22.1	66.7
$C_{max\ (ng/mL)}$	21.2	31.3
$T_{max\ (mn)}$	5.0	5.0
$AUC_{0\text{-}tlast\ (ng.h/mL)}$	19.2	30.3
$V_{\ (mL/kg)}$	19200	7390
$Cl_{\ (mL/h/kg)}$	6350	4680

5.2 Toxicokinetics

Refer to Section 6.2 Repeat Dose Toxicity for description of toxicokinetic information.

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose toxicology studies were not conducted.

6.2 Repeat-Dose Toxicity

Repeat-dose dermal toxicity studies included evaluation of systemic endpoints, up to 6 months in rats and 9 months in minipigs. The 6-month dermal rat study evaluated doses up to the maximum tolerated dose using 0.25% oxymetazoline cream, and the 9-month dermal minipig study evaluated concentrations as high as 2.5% oxymetazoline HCl cream. In the 6-month dermal rat study, oxymetazoline HCl treatment related effects included ulceration, erythema, hypertrophy of the tail artery, and diffuse myofibre atrophy at 0.1% and 0.25% oxymetazoline HCl cream, prominently in females. In the 9-month dermal minipig study, transient erythema and edema was observed at concentrations up to 2.5% oxymetazoline HCl cream.

Dermal application of oxymetazoline HCl cream, once-a-day using a semi-occlusion period of 6 hours, was locally tolerated at concentrations of up to 0.5% in rats and 2.5% in minipigs. Dermal studies in minipigs evaluated concentrations ranging from 0.25% to 2.5% oxymetazoline HCl cream. Drug-related effects seen in these studies were limited to erythema and edema at the application sites in minipigs given ≥0.25% oxymetazoline HCl cream. While these effects occasionally reached a moderate level of severity at the early part of the study, they subsided with continued dosing, suggesting adaptation to treatment. Dermal studies in rats showed mild transient erythema observed at ≥0.1% oxymetazoline HCl cream was also shown to subside with continued dosing. Slightly increased severity of acanthosis was noted at the application sites of drug- and vehicle-treated animals relative to sham controls.

Evidence of systemic toxicity due to dermal application of oxymetazoline HCl cream was limited to tail lesions in rats at 0.25% oxymetazoline HCl cream. Morbidity due to tail lesions necessitating euthanasia occurred in several females in the 6-month dermal rat study. Grossly observable tail lesions included tail tip necrosis, scabbing, and reddened or blackened tail tips. Microscopically, these gross changes were associated with ulceration, scabbing, and chronic inflammation. These gross and histologic changes are compatible with vasoconstriction of the rat tail and are consistent with the known pharmacological action of oxymetazoline as a potent agonist of both alpha1A adenoreceptor and serotonin receptors. The occurrence of vasoconstriction in the rat tail is further consistent with the known distribution of alpha1A adenoreceptors in the rat tail artery.

No evidence of systemic toxicity was observed in minipigs up to the highest tested dose using 2.5% oxymetazoline HCl cream for up to 9 months.

7 Genetic Toxicology

The sponsor submitted a standard battery of genotoxicity studies conducted with oxymetazoline HCl, including an in vitro bacterial reverse mutation test (i.e. Ames assay), an in vitro mammalian cell cytogenetic test: human lymphocyte (i.e. a chromosomal aberration test), and an in vivo oral (gavage) mouse micronucleus test. Oxymetazoline HCl showed no evidence of genotoxicity based on the results of these studies.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)
Study title: Bacterial reverse mutation test
Oxymetazoline HCl tested to the limit of cytotoxic concentration in a spectrum of *Salmonella typhimurium* strains and one *E. coli* strain did not increase the number of revertant colonies with or without metabolic activation; therefore, the drug was considered to be non-mutagenic.

7.2 *In Vitro* Assays in Mammalian Cells
Study title: *In vitro* mammalian cell cytogenetic test: Human lymphocyte
Under the assay conditions (with/without metabolic activation system), oxymetazoline HCl tested non-clastogenic.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title: Oral (gavage) mouse micronucleus test
There was no evidence of clastogenicity or aneugenicity up to maximum tolerated dose of 2.5 mg/kg/day; at this dose level, the mean plasma drug level was 8.83 ng/mL indicating sufficient drug exposure to the bone marrow.

All the above genetic toxicity studies were reviewed under the corresponding IND.

8 Carcinogenicity

The sponsor was granted a waiver for conduct of a dermal rat carcinogenicity study with oxymetazaline hydrochloride cream. The basis for the waiver was the extent of systemic toxicity noted after dermal administration of oxymetazoline hydrochloride cream in a 6 month dermal rat toxicity sudy. The primary toxicity noted in the 6 month dermal rat toxicity study was tail lesions at 0.25% oxymetazoline hydrochloride cream. Morbidity due to tail lesions necessitating euthanasia occurred in several females in the 6-month dermal rat study. Grossly observable tail lesions included tail tip necrosis, scabbing, and reddened or blackened tail tips. Microscopically, these gross changes were associated with ulceration, scabbing, and chronic inflammation. These gross and histologic changes are compatible with vasoconstriction of the rat tail and are consistent with the known pharmacological action of oxymetazoline as a potent agonist of both alpha1A adenoreceptor and serotonin receptors. The occurrence of vasoconstriction in the rat tail is further consistent with the known distribution of alpha1A adenoreceptors in the rat tail artery. The extent of tail lesions noted in the six month dermal rat toxicity

study would not be tolerated in a 2 year dermal rat carcinogenicity study. Therefore, the sponsor was granted a waiver for conduct of a 2 year dermal rat carcinogenicity study.

The sponsor did conduct a Tg.rasH2 mouse carcinogenicity study with oral administration of oxymetazoline hydrochloride. This study is reviewed below and the Exec CAC meeting minutes for this study are presented in Appendix 3.

Study title: Oxymetazoline HCl: 26-week oral carcinogenicity study in Tg.rasH2 mice

Study no.:	TX12006 / AD32ER.7G8R.BTL
Study report location:	SDN 1, electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 06, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Oxymetazaline HCl, Lot# R20751 / 010419AX21, 99.8%
CAC concurrence:	Yes, 5-31-12

Key Study Findings

No treatment related neoplastic findings were noted in this study. A treatment related increased incidence of non-neoplastic lesions was noted in kidney, brain and mesenteric lymph nodes.

Adequacy of Carcinogenicity Study

The carcinogenicity study appears to be adequate.

Appropriateness of Test Models

Conduct of a transgenic carcinogenicity study in mice is appropriate for the proposed drug product to evaluate possible systemic tumors if adequate systemic exposure is achieved after topical administration. The Tg.rasH2 mouse model is recommended for genotoxic and nongenotoxic carcinogen identification. This short-term carcinogenicity assay is an acceptable alternative to the traditional two-year mouse carcinogenicity assay as described in the ICH S1B document.

Evaluation of Tumor Findings

No treatment related tumors were noted in this study.

The tumor incidences were within the historical control ranges from the testing laboratory. No statistically significant increase in tumors was observed in groups treated with oxymetazoline HCl. Treatment with urethane (positive control) produced a high incidence of lung tumors and splenic hemangiosarcomas.

Methods

Doses:	0 (vehicle control), 0.5, 1.0 and 2.5 mg/kg/day oxymetazoline HCl; 1000 mg/kg/day urethane ip on days 1, 3, and 5 (positive control)
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg/day
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Sterile Water
Basis of dose selection:	MTD based on renal toxicity noted in a 28-day oral dose range finding study conducted in CByB6F1 wild type mice. Mild to moderate kidney infarction with minimal to mild renal arterial degeneration/necrosis and periarteritis was observed microscopically at ≥ 2.5 mg/kg/day
Species/Strain:	Mouse / Main study: Tg.rasH2 [CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)]; Positive control: Tg.rasH2; TK: CByB6F1, wild-type
Number/Sex/Group:	25
Age:	8 weeks; Males: 20.6 – 25.9 grams; Females: 15.7 – 20.7 grams
Animal housing:	Single animal housing
Paradigm for dietary restriction:	N/A
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	TK: 12/sex/group for the vehicle group and 25/sex/group for test article groups; Positive Control: 10/sex/group
Deviation from study protocol:	None of significance

The study design is described in the following table.

Group	Oxymetazoline HCl Dose Levels (mg/kg/day)**	Number of Animals			
		Main Cohort (Tg.rasH2)		TK Cohort*** (CByB6F1)	
		Male	Female	Male	Female
1	0	25	25	12	12
2	0.5	25	25	25	25
3	1.0	25	25	25	25
4	2.5	25	25	25	25
5*	1000 (Urethane)	10	10	0	0
Total		110	110	87	87

*Group 5 Positive Control animals were administered a total of 3 intraperitoneal (i.p.) injections (one injection each day on Days 1, 3, and 5) using a dose volume of 10 mL/kg/injection.
** Were administered once daily by oral gavage using a dose volume of 10 mL/kg.
***Extra TK Cohort animals were used to ensure adequate numbers of animals were available for bleeding.

Observations and Results

Mortality

Mortality was assessed twice daily.

There was no statistically significant dose response in mortality across the treatment groups in either sex. There were no statistically significant decreases in mortality in any treated group in either sex compared to their respective control. The 2.5 mg/kg/day male mortality with the kidney infarct as cause of death is considered to be drug-related. The other 2.5 mg/kg/day male mortality with necrosis and degeneration noted in the spinal cord may not be due to drug effect, given the clinical signs of impaired gait of both hind legs, age of the mouse and dorsal and bilateral nature of the lesion. However, the possibility of these spinal cord lesions induced by the drug cannot be completely ruled out.

The summary of mortality data is provided in the following table (copied from NDA submission).

Text Table 1: Main Cohort Mortality

Group (Dose)	Mode of Death	Animal Number	Sex	Day of Death	Cause of Death
Group 1 (0 mg/kg/day)	Moribund Sacrifice	6702	Male	92	Lung, carcinoma
Group 1 (0 mg/kg/day)	Natural Death	6704	Male	165	Skin, hemangiosarcoma
Group 2 (0.5 mg/kg/day)	Moribund Sacrifice	6746	Male	134	Lung, carcinoma Spleen, hemangiosarcoma
Group 3 (1.0 mg/kg/day)	Natural Death	6755	Male	158	Multicentric lymphoma
Group 4 (2.5 mg/kg/day)	Moribund Sacrifice	6778	Male	80	Kidney, infarcts
Group 4 (2.5 mg/kg/day)	Moribund Sacrifice	6788	Male	22	Spinal cord, necrosis and degeneration
Group 1 (0 mg/kg/day)	Moribund Sacrifice	6832	Female	99	Undetermined
Group 3 (1.0 mg/kg/day)	Natural Death	6868	Female	60	Undetermined
Group 4 (2.5 mg/kg/day)	Moribund Sacrifice	6888	Female	159	Salivary gland, hemangiosarcoma

Table 3: Intercurrent Mortality Rate -Male Mice

	0 mg|kg|day		0.5 mg|kg|day		1.0 mg|kg|day		2.5 mg|kg|day		1000 mg|kg Positive Control	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	.	.	2	8.00	.	.
14 - 26	2	8.00	1	4.00	1	4.00	.	.	1	10
Ter.Sac.(week 18)	.	.	.	.	.	.	.	.	9	90.00
Ter.Sac.(week 27)	23	92.00	24	96.00	24	96.00	23	92.00	.	.
	N=25		N=25		N=25		N=25		N=10	

Cum. %: Cumulative percentage except for Ter. Sac.

Table 4: Intercurrent Mortality Rate -Female Mice

	0 mg|kg|day		0.5 mg|kg|day		1.0 mg|kg|day		2.5 mg|kg|day		1000 mg|kg Positive Control	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	1	4.00	1	4.00	.	.
14 - 26	1	4.00	.	.	.	.	1	4.00	1	10
Ter.Sac.(week 18)	.	.	.	.	.	.	.	.	9	90.00
Ter.Sac.(week 27)	24	96.00	25	100.00	24	96.00	24	96.00	.	.
	N=25		N=25		N=10		N=25		N=10	

Cum. %: Cumulative percentage except for Ter. Sac.

Clinical Signs

Clinical signs were assessed once daily on all Main Cohort animals.

Drug-related tremors during the first 20 days of dosing and piloerection throughout the dosing period were noted in both sexes at all doses with oxymetazoline HCl.

At 2.5 mg/kg/day, drug-related effects included ruffled fur in both sexes, rapid and shallow respiration observed in males and a hunched posture in males and females.

Body Weights

Body weights were assessed weekly for the first 13 weeks and biweekly thereafter on all animals.

Drug-related decreases in mean body weights were noted in males given 1.0 and 2.5 mg/kg/day as compared to the vehicle control group. No treatment related effects on body weight were noted in females.

Male and female body weight curves are provided below (copied from NDA submission).

FIGURE 1- GROUP MEAN BODY WEIGHTS FOR MALES

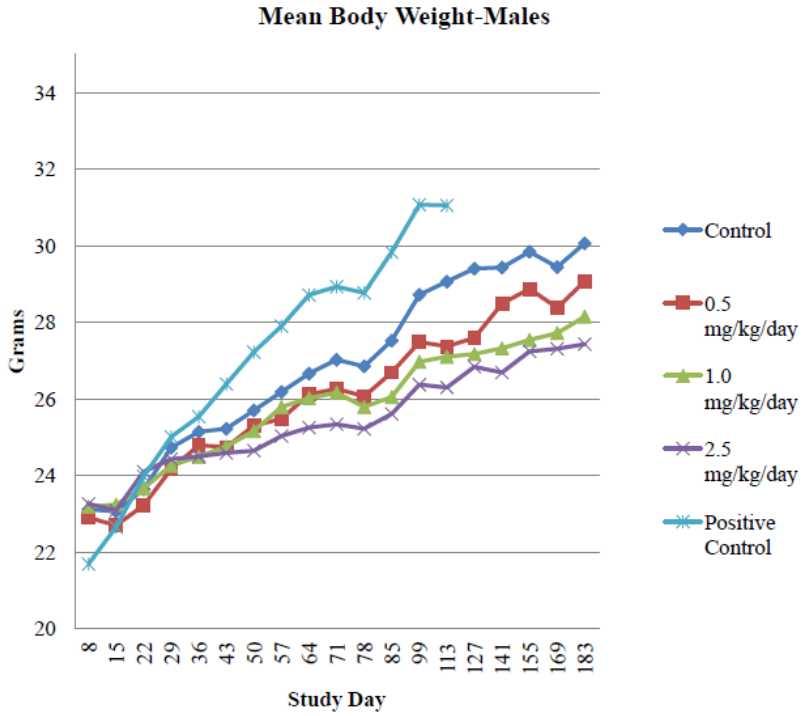
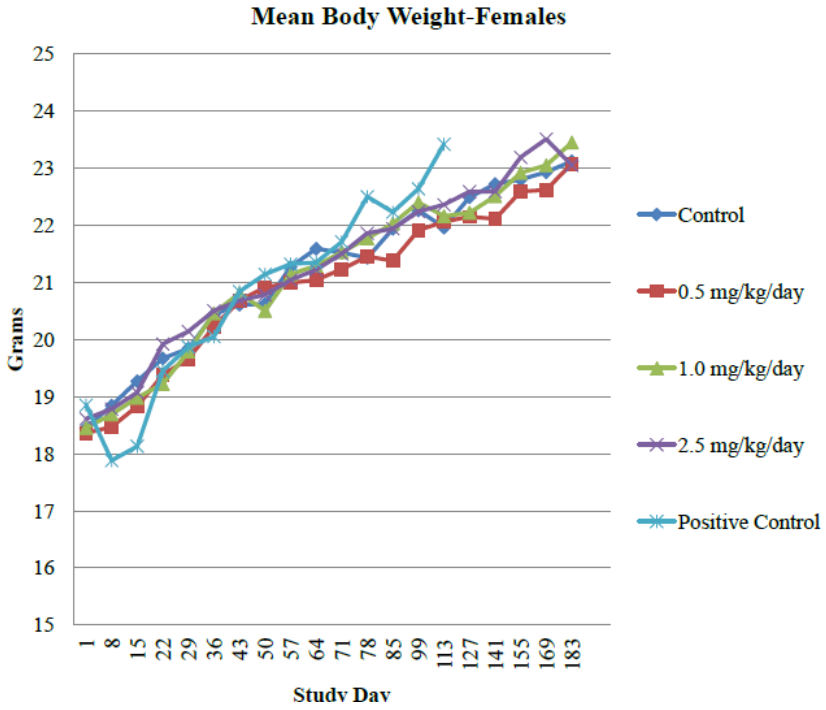


FIGURE 2- GROUP MEAN BODY WEIGHTS FOR FEMALES



Feed Consumption

Food consumption was assessed weekly on Main Cohort animals.
No treatment related effects on food consumption was noted in this study.

Gross Pathology

A complete gross necropsy with collection of tissues was performed for all animals in Main Cohort groups at the end of treatment.

Gross lesions in the kidneys such as discoloration, mottling, small size and/or deformity were noted in 9/25 males and 3/25 females at 2.5 mg/kg/day.

Organ Weights

The adrenal glands, brain, heart, kidneys, liver, spleen, and testes/ovaries were weighed for all Main Cohort animals at necropsy.

Decreases in kidney weights (4-14%) were observed in males at ≥ 1.0 mg/kg/day and females at 2.5 mg/kg/day. These decreases may be related to the infarcts noted in the kidneys, which was further verified by comparing the individual kidney weights with those exhibiting infarcts.

Minimal absolute or relative organ weight changes (≤10%) were observed in liver (↓), testicular (↓) or heart (↑), however there were no microscopic lesions that were associated with these variations.

The summaries of statistically significant differences in the absolute and relative organ weights are presented in the following table (copied from the NDA submission).

Text Table 2A: Male Absolute Organ Weights

Parameter	Dose Level (mg/kg/day)	Significant Difference Compared to Control (Group 1)	% Difference from Group 1 (%)
Terminal Body Weight	2.5	↓	9
Kidneys	1.0 & 2.5	↓	7 & 14
Liver	1.0 & 2.5	↓	7 & 8
Testes	2.5	↓	5

↓ = statistically significant decrease when compared to 0 mg/kg/day.
Group 1 - 0 mg/kg/day (Vehicle) Group 2 - 0.5 mg/kg/day
Group 3 - 1.0 mg/kg/day Group 4 - 2.5 mg/kg/day

Text Table 2B: Male Relative Organ Weights

Parameter	Dose Level (mg/kg/day)	Significant Difference Compared to Control (Group 1)	% Difference from Group 1 (%)
Relative Heart	0.5, 1.0, & 2.5	↑	7, 10 & 10
Relative Kidneys	2.5	↓	6

↑= statistically significant increase when compared to 0 mg/kg/day.
↓ = statistically significant decrease when compared to 0 mg/kg/day.
Group 1 - 0 mg/kg/day (Vehicle) Group 2 - 0.5 mg/kg/day
Group 3 - 1.0 mg/kg/day Group 4 - 2.5 mg/kg/day

Text Table 3: Female Relative Organ Weights

Parameter	Dose Level (mg/kg/day)	Significant Difference Compared to Control (Group 1)	% Difference from Group 1 (%)
Relative Kidneys	2.5	↓	4
Relative Liver	1.0	↓	6

↓ = statistically significant decrease when compared to 0 mg/kg/day.
Group 1 - 0 mg/kg/day (Vehicle) Group 2 - 0.5 mg/kg/day
Group 3 - 1.0 mg/kg/day Group 4 - 2.5 mg/kg/day

Histopathology

The following tissues were collected for histopathological evaluation: adrenal gland, aorta, bone (femur, sternum), bone marrow (sternum), brain, cervix, epididymis, esophagus, eyes, gall bladder, harderian gland, heart, intestine (cecum, colon, duodenum, ileum, jejunum, rectum), kidneys, liver, lung and bronchi, lymph node (mandibular, mesenteric), mammary gland, nasal cavity, nerve (sciatic), ovaries, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicles, skeletal muscle (thigh), skin (mammary), spinal cord (cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina and gross lesions/masses.

Histopathological evaluation was performed on all collected tissues from all Main Cohort animals, as well as on the lung and spleen from all positive control animals.

Peer Review
Yes

Neoplastic and non-neoplastic findings

(1) Neoplastic changes

No treatment related neoplastic lesions were noted in this study.
The CDER statistical reviewer, Dr. Zhuang Miao, generated the following table in his review that lists the potentially statistically significant results for organ-tumor combinations.

Table 7: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons -Male Mice

Organ Name	Tumor Name	0 mg|kg|day Vehicle Cont N=25	0.5 mg|kg|day Low N=25	1.0 mg|kg|day Med N=25	2.5 mg|kg|day High N=25	P_Value Dose Resp	P_Value VC vs. L	P_Value VC vs. M	P_Value VC vs. H
ear	papilloma	0	1	0	0	0.7500	0.5000	.	.
lungs with bronchi	alveolar-bronchiolar adenoma	4	4	1	3	0.6883	0.6496	0.9777	0.7743
	alveolar-bronchiolar carcinoma	1	2	0	0	0.9356	0.5000	1.0000	1.0000
	alveolar_carci+ade	**5**	**6**	**1**	**3**	**0.8389**	**0.5000**	**0.9889**	**0.8491**
skin	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
spleen	hemangiosarcoma	2	1	2	2	0.4206	0.8901	0.7110	0.6794
multicentric	lymphoma	0	0	1	0	0.5000	.	0.5000	.
stomach	papilloma	0	0	0	1	0.2396	.	.	0.4894
Multiple Organs	**hemangiosarcoma/hemangioma**	**3**	**1**	**2**	**2**	**0.5770**	**0.9498**	**0.8384**	**0.8130**

Table 8: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons -Female Mice

Organ Name	Tumor Name	0 mg|kg|day Vehicle Cont N=25	0.5 mg|kg|day Low N=25	1.0 mg|kg|day Med N=25	2.5 mg|kg|day High N=25	P_Value Dose Resp	P_Value VC vs. L	P_Value VC vs. M	P_Value VC vs. H
harderian glands	adenoma	0	1	1	0	0.6314	0.5102	0.5000	.
	carcinoma	1	0	1	0	0.8157	1.0000	0.7553	1.0000
	carcinoma/adenoma	**1**	**1**	**2**	**0**	**0.8131**	**0.7653**	**0.5000**	**1.0000**
lungs with bronchi	alveolar-bronchiolar adenoma	1	0	5	2	0.2557	1.0000	0.0941	0.5156
	alveolar_carci+ade	**1**	**0**	**5**	**2**	**0.2557**	**1.0000**	**0.0941**	**0.5156**
lymph node, mandibul	lymphangioma	0	1	1	0	0.6314	0.5102	0.5000	.
salivary glands	hemangiosarcoma	0	0	0	1	0.2551	.	.	0.5102
skin	hemangiosarcoma	0	1	0	0	0.7551	0.5102	.	.
	squamous cell carcinoma	0	0	0	1	0.2551	.	.	0.5102
spleen	hemangiosarcoma	1	0	4	1	0.4544	1.0000	0.1738	0.7653
thymus	thymoma	0	0	1	0	0.5000	.	0.5000	.
uterus	endometrial stromal polyp	0	0	0	1	0.2551	.	.	0.5102
Multiple Organs	**hemangiosarcoma/hemangioma**	**1**	**1**	**4**	**2**	**0.3185**	**0.7653**	**0.1738**	**0.5156**

The tumors identified by Dr. Miao in the above table are considered common tumors. There was an increase in the incidence of lung adenomas and the combined incidence of lung adenomas and carcinomas in the mid-dose females. However, this increase was not statistically significant and were not considered to be drug-related because: a) the incidence of both adenomas and carcinomas fell within the historical control range; b) the statistically significant increase was in a single group and not dose dependent. The CDER Executive Carcinogenicity Assessment Committee (eCAC) criteria for considering a common tumor as treatment related is that both the trend and pairwise comparison for high dose versus vehicle have a p-value less than 0.01. None of the tumors listed in the previous table meet this criteria.

The positive group showed statistically significant increases in alveolar-bronchiolar adenoma and alveolar-bronchiolar carcinoma, and hemangiosarcoma in lungs with bronchi, hemangiosarcoma in spleen for both male and female mice. Dr. Miao

generated the following tables in his review that lists the statistically significant neoplastic findings in positive control mice compared to vehicle control mice.

Table 9: Tumor Rates and P-Values for Comparison between Vehicle Control and Positive Control -Male Mice

Organ Name	Tumor Name	0 mg|kg|day Vehicle Cont N=25	1000 mg|kg Positive Cont N=10	P_Value VC vs. PC
ear	papilloma	0	0	.
lungs with bronchi	alveolar-bronchiolar adenoma	4	10	<0.001*
	alveolar-bronchiolar carcinoma	1	5	<0.001*
	hemangiosarcoma	0	3	0.0027*
skin	hemangiosarcoma	1	0	1.0000
spleen	hemangiosarcoma	2	9	<0.001*

Table 10: Tumor Rates and P-Values for Comparison between Vehicle Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg|kg|day Vehicle Cont N=25	1000 mg|kg Positive Cont N=10	P_Value VC vs. PC
harderian glands	adenoma	0	0	.
	carcinoma	1	0	1.0000

Organ Name	Tumor Name	0 mg|kg|day Vehicle Cont N=25	1000 mg|kg Positive Cont N=10	P_Value VC vs. PC
lungs with bronchi	alveolar-bronchiolar adenoma	1	10	<0.001*
	alveolar-bronchiolar carcinoma	0	8	<0.001*
	hemangiosarcoma	0	2	0.0159*
lymph node, mandibul	lymphangioma	0	0	.
skin	hemangiosarcoma	0	0	.
spleen	hemangiosarcoma	1	10	<0.001*
thymus	thymoma	0	0	.

(2) Non-neoplastic changes

Dose-dependent non-neoplastic lesions were noted in the kidney, brain and mesenteric lymph nodes. The lesions in kidneys and brain were considered to be possibly induced by underlying vascular lesions or vasoconstrictive pharmacological effects of the drug.

Kidney

The non-neoplastic lesions observed in kidneys included unilateral or bilateral infarcts that consisted of mostly focal, wedge shaped lesions in the cortex just beneath the capsule. The infarcts included degenerate tubules with vacuolation and attenuation of epithelial cells, tubules with necrotic epithelial cells, mineralized tubules, tubules with presence of proteinaceous material and regenerating tubules characterized by increased basophilia and crowding of hyperchromatic nuclei. In these infarcts, there was occasional fibrosis and infiltration of few mixed inflammatory cells. Unilateral infarction noted in 1 female mouse of the vehicle control group was considered to be an incidental finding.

The summary of these findings in kidney are shown in the following table (copied from the NDA submission).

Text Table 15: Incidence of Kidney Infarcts

MALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Bilateral				
Mild	0	0	0	1
Moderate	0	0	1	4
Unilateral				
Minimal	0	0	1	2
Mild	0	0	0	5
Moderate	0	0	1	1
Combined Incidence	0	0	3	13
FEMALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Bilateral				
Minimal	0	0	0	1
Mild	0	0	0	2
Moderate	0	0	0	1
Unilateral				
Minimal	0	0	0	1
Mild	1	0	0	2
Moderate	0	0	0	2
Marked	0	0	0	1
Combined Incidence	1	0	0	10

Brain:

The non-neoplastic lesions observed in brain included unilateral or bilateral infarcts that consisted of neuronal necrosis, degeneration and/or gliosis of minimal to mild severity noted in the hippocampal region in 3 males and 4 females at 2.5 mg/kg/day. In addition, minimal degeneration was noted in the cerebral cortex of 1 male at 2.5 mg/kg/day, and mild necrosis was noted in the cerebellum of another male in the same dose group.

The summary of these finding in brain are shown in the following table (copied from the NDA submission).

Text Table 16: Incidence of Brain Lesions

MALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Hippocampus				
Necrosis				
Mild	0	0	0	2
Degeneration				
Mild	0	0	0	3
Gliosis				
Mild	0	0	0	1
Cerebral Cortex				
Degeneration				
Minimal	0	0	0	1
Cerebellum				
Necrosis				
Mild	0	0	0	1
Combined Incidence	0	0	0	5
FEMALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Hippocampus				
Necrosis				
Minimal	0	0	0	1
Mild	0	0	0	2
Degeneration				
Minimal	0	0	0	1
Gliosis				
Mild	0	0	0	1
Combined Incidence	0	0	0	4

Mesenteric lymph nodes:
The non-neoplastic lesions in mesenteric lymph node consisted of plasmacytosis and infiltration of neutrophils in males at ≥ 1.0 mg/kg/day and in females at ≥ 0.5 mg/kg/day. The summary of this finding is shown in the following table (copied from the NDA submission).

Text Table 17: Incidence of Mesenteric Lymph Node Lesions

MALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Plasmacytosis				
Minimal	0	0	4	0
Mild	0	0	3	4
Moderate	0	0	1	1
Infiltration, Neutrophils				
Minimal	0	0	5	1
Mild	0	0	0	2
Moderate	0	0	1	0
FEMALES				
Dose (mg/kg/day)	0	0.5	1.0	2.5
Plasmacytosis				
Minimal	0	1	0	0
Mild	0	2	7	6
Moderate	0	1	0	4
Infiltration, Neutrophils				
Minimal	0	1	0	0
Mild	0	1	3	4
Moderate	0	0	1	0

Toxicokinetics

Blood samples for toxicokinetic assessment were collected from 3 TK animals/sex/group/timepoint on Day 30 at 0.5 hour post dose and Day 177 at pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose.

The toxicokinetic parameters determined from this study are provided in the following table (copied from the NDA submission).

Text Table 9: Summary of TK Parameters

Gender	Dose (mg/kg /day)	C_{max} (ng/mL)		T_{max} (hr)	AUC_{0-t} (ng•hr/mL)		AUC Interval (hr)	C_{max}/ Dose	AUC_{0-t} /Dose
		Mean	SD	Mean	Mean	SE			
Day 30									
Male	0.5	0.334	0.121	0.500	NC*	NC*	NC*	0.668	NC*
	1.0	1.31	0.0896	0.500	3.52	0.404	(0-8 Hours)	1.31	3.52
	2.5	6.41	2.65	0.500	16.9	1.61	(0-8 Hours)	2.56	6.76
Female	0.5	0.315	0.120	0.500	NC*	NC*	NC*	0.630	NC*
	1.0	1.30	0.436	0.500	2.42	0.314	(0-8 Hours)	1.30	2.42
	2.5	5.40	1.96	0.500	12.8	2.58	(0-8 Hours)	2.16	5.12
Overall	0.5	0.324	0.108	0.500	NC*	NC*	NC*	0.648	NC*
	1.0	1.30	0.282	0.500	2.97	0.281	(0-8 Hours)	1.30	2.97
	2.5	5.90	2.16	0.500	14.8	1.56	(0-8 Hours)	2.36	5.92
Day 177									
Male	0.5	0.690	0.352	0.500	1.26	0.238	(0-4 Hours)	1.38	2.52
	1.0	1.84	0.703	0.500	4.89	0.644	(0-8 Hours)	1.84	4.89
	2.5	10.4	5.10	0.500	19.9	1.87	(0-8 Hours)	4.16	7.96
Female	0.5	0.354	0.185	0.500	0.390	0.0840	(0-2 Hours)	0.708	0.780
	1.0	2.00	1.53	0.500	3.43	0.298	(0-8 Hours)	2.00	3.43
	2.5	3.98	1.16	0.500	12.1	0.713	(0-8 Hours)	1.59	4.84
Overall	0.5	0.522	0.312	0.500	0.924	0.147	(0-4 Hours)	1.04	1.85
	1.0	1.92	1.07	0.500	4.16	0.366	(0-8 Hours)	1.92	4.16
	2.5	7.20	4.83	0.500	15.9	1.24	(0-8 Hours)	2.88	6.36

N = 3/sex/time point;

The concentrations of Oxymetazoline in vehicle control group were all below the limit of quantitation.

*NC = Not Calculated. AUC was not calculated because there were fewer than 3 consecutive concentrations above the lower limit of quantitation for accurate AUC determination.

There was no gender differences in systemic exposure noted in this study. Systemic exposure of oxymetazoline HCl increased with increasing dose. No apparent dose accumulation between Day 30 to Day 177 was noted in this study.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 98.6 to 101.0%, which is acceptable.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

An oral (gavage) fertility and early embryonic development study has been conducted in rats. The study has been reviewed under the corresponding IND.

Oxymetazoline HCl was administered once daily by oral gavage to Sprague-Dawley rats (20/group) at 0 (vehicle), 0.05, 0.1, or 0.2 mg/kg/day. Males were treated for 14 days prior to mating, during mating, and until the day prior to necropsy (approximately two weeks after the mating period). Females were treated for 14 days before mating, during mating, and until gestation day 6 (GD 6). Females were necropsied on GD 13. Decreased number of corpora lutea and increased post-implantation losses were recorded in the high-dose females; however, drug had no effect on the fertility and mating parameters. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for early embryonic development was established at the high-dose of 0.2 mg/kg/day.

Toxicokinetic assessment was not performed in the oral rat fertility and early embryonic development study. Therefore, the AUC values noted in the oral rat embryofetal development study, which was conducted at the same dose levels, will be used for calculation of multiples of human exposure for this study in the label.

9.2 Embryonic Fetal Development

9.2.1. An oral (gavage) developmental toxicity study with toxicokinetic sampling has been conducted in rats. The study has been reviewed under the corresponding IND.

Oxymetazoline HCl at 0.05, 0.1 or 0.2 mg/kg/day was administered once daily by oral gavage to Crl:CD(SD) rats from gestation days (GD) 6 to 17. Adverse effects were restricted to the high-dose females. No external, visceral, and skeletal abnormalities were found in fetuses at any dose level. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for rat embryo-fetal development toxicity was established at the high-dose of 0.2 mg/kg/day. The C_{max} and $AUC_{0\text{-}tlast}$ at 0.2 mg/kg/day were 0.541 ng/mL and 3.43 ng.hr/mL on GD day 17, respectively. The C_{max} and $AUC_{0\text{-}tlast}$ at 0.1 mg/kg/day were 0.324 ng/mL and 1.77 ng.hr/mL on GD 17, respectively.

9.2.2. An oral (gavage) embryo-fetal development study has been conducted in rabbits. The study has been reviewed under the corresponding IND.

Oxymetazoline HCl was administered to New Zealand White (NZW) rabbits once daily by oral gavage at 0.1, 0.5, or 1.0 mg/kg/day from GD 6 to 18. The incidence of minor fetal abnormalities and variations related to skeletal ossification at high dose level were considered to be secondary changes associated with much reduced maternal food consumption and body weight. The NOAEL for rabbit maternal and embryo-fetal development toxicity was 0.5 mg/kg/day and 1.0 mg/kg/day, respectively. The C_{max} at

1.0 mg/kg/day was 14.4 ng/mL on GD day 16. The AUC_{0-24} at 1.0 mg/kg/day was 76.2 ng.hr/mL on GD day 16. The C_{max} at 0.5 mg/kg/day was 4.59 ng/mL on GD day 16. The AUC_{0-24} at 1.0 mg/kg/day was 28.2 ng.hr/mL on GD day 16.

9.3 Prenatal and Postnatal Development

Study Title: Oxymetazoline HCl: Oral Prenatal and Postnatal Developmental Study in Rats

Study no.:	20053293 (Sponsor Ref. No. TX14034)
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 6th, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Oxymetazoline HCl, 016829AX20, 101.0%

Key study findings:

- Oral doses of 0 (vehicle), 0.05, 0.1 and 0.2 mg/kg/day oxymetazoline HCl were administered to pregnant female Sprague-Dawley rats once daily on gestation days (GD) 6 through postpartum day (PPD) 20.
- F0 findings: Slight decreases in body weight, body weight gains, as well as food consumption were observed at 0.2 mg/kg/day. Pharmacologic effects of oxymetazoline on clinical observations were noted at ≥0.05 mg/kg/day. No treatment related effects on F0 maternal reproductive performance or macroscopic parameters were noted. The maternal NOAEL was identified as 0.1 mg/kg/day.
- F1 findings: Increases in pup mortality at 0.2 mg/kg/day and decreased pup weights, necropsy observations, and delayed sexual maturation at ≥0.1 mg/kg/day. The prenatal and developmental NOAEL was identified as 0.05 mg/kg/day. The mean plasma concentration 30 minutes post pose at 0.05 mg/kg/day was 0.252 ng/mL.
- F2 findings: There were no treatment related effects noted in the study.
- TK analysis: All test article treated dams were exposed to oxymetazoline HCl. The mean plasma concentrations increased in a dose proportional manner from 0.05 to 0.1 mg/kg/day, and in a less than dose proportional manner from 0.1 to 0.2 mg/kg/day. Mean maternal milk concentrations increased in a generally dose proportional manner in all test article-treated groups.

Methods

Doses:	0 (vehicle control), 0.05, 0.1, 0.2 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous solution/Deionized water
Species/Strain:	Rats / Crl:CD(SD) Sprague-Dawley

Number/Sex/Group:	22 F0 Females per group
Satellite groups:	TK: 4 F0 females per group
Study design:	*Main study rats:* 88 pregnant female (F0 generation dam) rats were randomly assigned to 4 groups (22 females per group). Test article or vehicle were administrated via oral gavage once daily from GD 6 through PPD 20 for rats that delivered a litter, or through GD 24 for rats that did not deliver a litter. *TK rats:* An additional 16 pregnant females rats were randomly assigned to 4 groups (4 rats/group) for TK sample collections. Test article and or vehicle were administrated via oral gavage once daily from GD 6 through PPD 14 for rats that delivered a litter or through GD 24 for rats that did not deliver a litter.
Parameters and endpoints evaluated:	*For F0 generation rats*, viabilities, clinical observations, observations of maternal behavior, body weights, food consumption, and natural delivery observations were recorded. F0 main study animals were sacrificed on PPD 28. F0 TK animals were sacrificed on PND 14. F0 animals that did not deliver were sacrificed on GD 25. Blood samples and milk samples were collected from up to 3 TK female rats assigned for TK sample collections on PPD 14. *For F1 generation rats*, viabilities, clinical observations, body weights, food consumption, sexual maturation, passive avoidance evaluations, water-maze, and reproductive capacity were recorded. All F1 pups not selected for continued evaluation were sacrificed and examined for gross lesions.
Deviation from study protocol:	None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Observations and Results:

F_0 Dams

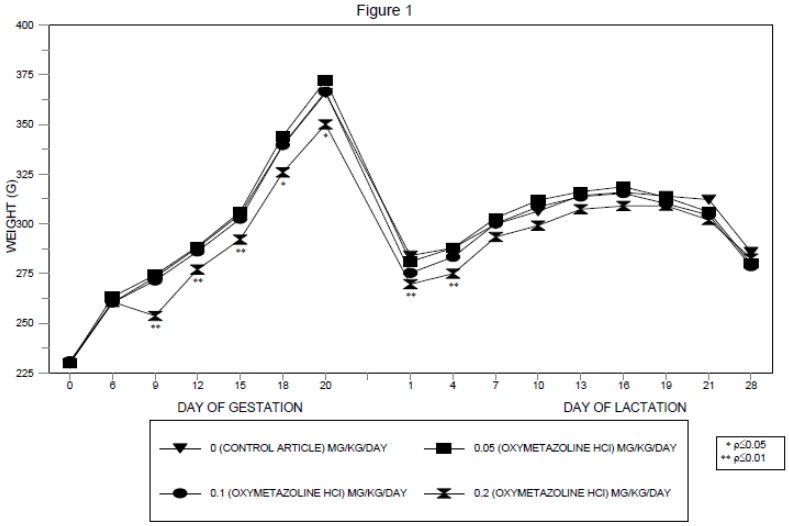
Survival:	Twice daily. Two F0 generation female rats, one in each of the 0.1 and 0.2 mg/kg/day dose groups, were found dead on PPD 18. The death in the 0.2 mg/kg/day dose group was secondary to an intubation error. The cause of the death at

0.1 mg/kg/day could not be determined based on the in-life and postmortem observations.

Clinical signs: Once daily. Piloerections were observed in all oxymetazoline-treated rats at 0.05, 0.1 and 0.2 mg/kg/day on most days of the gestation dosing period. It persisted into the lactation period in all rats that delivered a litter. This sign is considered as the pharmacologic effects of oxymetazoline. Mild dehydration, hunched posture, and thin body condition were observed at 0.2 mg/kg/day during the gestation period.

Body weight: GD 0, 6, 9, 12, 15, 18, 20 and 25 (if applicable) and PPD 1, 4, 7, 10, 13, 16, 19, 21 and 28. Maternal body weights and body weight gains were unaffected at up to 0.1 mg/kg/day. Transient body weight loss was observed on GD 6-9 at 0.2 mg/kg/day. For the entire gestation dosing period (GD 6 to 20), the maternal body weight at 0.2 mg/kg/day was 96% of the control group value and the corresponding body weight gains were 85% of the control group value.
The below figure adapted from the submission showed the maternal body weights during the study.

MATERNAL BODY WEIGHTS - F0 GENERATION FEMALE RATS
Figure 1



Food consumption: GD 0, 6, 9, 12, 15, 18, 20 and 25 (if applicable) and PPD 1, 4, 7, 10, and 14. No treatment-related effects on food consumption were observed at up to 0.1 mg/kg/day. Transient decreases in maternal food consumption (↓~50%) were observed at 0.2 mg/kg/day

on GD 6 to 9 when compared to the control group. Absolute maternal food consumption at 0.2 mg/kg/day was 87% and 91% of the control group value for the entire gestation period and lactation period, respectively.

Natural delivery observation: Pregnancy occurred in 19 (86.4%), 20 (90.9%), 21 (95.4%) and 20 (90.9%) of the 22 female rats in the 0, 0.05, 0.1, and 0.2 mg/kg/day dose groups, respectively. All pregnant dams delivered litters, with the exception of one control group dam.

Increased pup mortality was observed at the 0.2 mg/kg/day maternal dosage. The lactation index (number of live pups on PPD 28/ number of live pups on PPD 4) was decreased by ~5% in the 0.2 mg/kg/day dose group when compared to the control group, reflecting 11 pup mortalities out of 256 live pups between PPD 8 and 14.

Dose dependent decreases in pup body weights were observed from PPD 1 through 28 at ≥0.05 mg/kg/day. The decreases tended to be more transiently pronounced as the lactation period continued. On PPD 1, pup body weights were 100%, 94%, and 94% of the control group value in the 0.05, 0.1, and 0.2 mg/kg/day dose groups, respectively. On PPD 28, pup body weights were 93%, 88%, and 73% of the control group value in the three respective test article-treated groups.

There were no treatment related effects on all other natural delivery and litter observations at doses of up to 0.2 mg/kg/day. Values for the numbers of dams delivering litters, the duration of gestation, averages for implantation sites per delivered litter, the gestation index, the numbers of dams with stillborn pups and of dams with all pups dying, litter sizes, viability index, surviving pups per litter, percent male pups per number of pups sexed per litter, and the live litter size at weighing were comparable among the four dose groups and did not significantly differ.

The table below showed a summary of these findings.

F0 generation female:	**0**	**0.05**	**0.1**	**0.2**

	mg/kg/day	**mg/kg/day**	**mg/kg/day**	**mg/kg/day**
Total # of rats / group	22	22	22	22
Pregnant rate	19 (86%)	20 (91%)	21 (95%)	20 (91%)
Delivered litter	18 (95%)	20 (100%)	21 (100%)	20 (100%)
Duration of gestation	22.6	22.6	22.5	22.6
Gestation index	95%	100%	100%	100%
Implantation sites per litter	244	289	300	283
Dams with stillborn pups	1 (6%)	2 (10%)	1 (5%)	2 (10%)
F1 generation litters:	**0 mg/kg/day**	**0.05 mg/kg/day**	**0.1 mg/kg/day**	**0.2 mg/kg/day**
Viability index	100%	99.2%	99.0%	99.6%
Lactation index	100%	99.6%	99.2%	94.6%
Pups delivered	223	264	288	260
Litter size (PPD 1) (PPD 28)	12.3 12.3	13.0 12.9	13.7 13.3	12.9 12.1
Pup weight (PPD 1) (PPD 28)	6.8 81.1	6.8 75.7	6.4 71.2	6.4 59.2

Necropsy observation: No treatment related necropsy observations were noted in F_0 females.

Toxicokinetics: PPD 14. Because there were fewer than 3 TK F0 dams with delivered litters in Group 3, blood samples were collected from a main study F0 rat (dam 9345, selected based on delivery date) with a delivered litter, in order to collect a total of 3 samples per time point in the affected group.

All test article-treated F_0 dams were exposed to oxymetazoline. The mean plasma concentrations 30 min post dosing increased in a dose proportional manner from 0.05 to 0.1 mg/kg/day, and in a less than dose proportional manner from 0.1 to 0.2 mg/kg/day. Mean maternal milk concentrations 1 hour post dosing increased in a generally dose proportional manner in all test article-treated groups.

The table below adapted from the submission showed the toxicokinetics results on plasma samples and milk samples. Complete toxicokinetic assessment was not conducted in this study. Therefore, the AUC values noted in the oral rat embryofetal development study, which was conducted at the same dose levels, will be used for calculation of multiples of human exposure for this study in the label.

Text Table 13
Summary of Oxymetazoline Concentrations in Rat Plasma on DL 14

Dose (mg/kg/day)	Mean Concentration (ng/mL)	
	Predose	30 -Minutes Postdose
0	BLQ	BLQ
0.05	BLQ	0.252 ± 0.746
0.1	BLQ	0.540 ± 0.096
0.2	BLQ	0.740 ± 0.174

N=3, BLQ = <0.0100

Text Table 12
Summary of Oxymetazoline Concentrations in Rat Milk on DL 14

Dose (mg/kg/day)	Mean Concentration (ng/mL)
0	BLQ
0.05	1.12 ± 0.23
0.1	2.46 ± 0.31
0.2	4.16 ± 2.40

N=3, BLQ = <0.0100

Dosing Solution Analysis The dosing solution was prepared fresh on each dosing day. All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 10% (individual values within or equal to ± 15%) of their theoretical concentrations.

F_1 Generation

Survival: Twice daily. No treatment related effects on mortality were noted in this study. All F1 generation rats survived to scheduled euthanasia.

Clinical signs: Once daily. Signs of cold to touch (N=9 of 20 litters), dehydrated (N=5 of 20 litters), thin body condition or not nesting (N=2 of 20 litters) were noted at 0.2 mg/kg/day maternal dose.

Body weight: Preweaning -PPD 1, 4, 7, 10, 14, 18, 21, and 28 (PPD 22 for pups selected for continued evaluation). Postweaning – DG 0, 3,6,9,12, 15,18 and 21 (females)

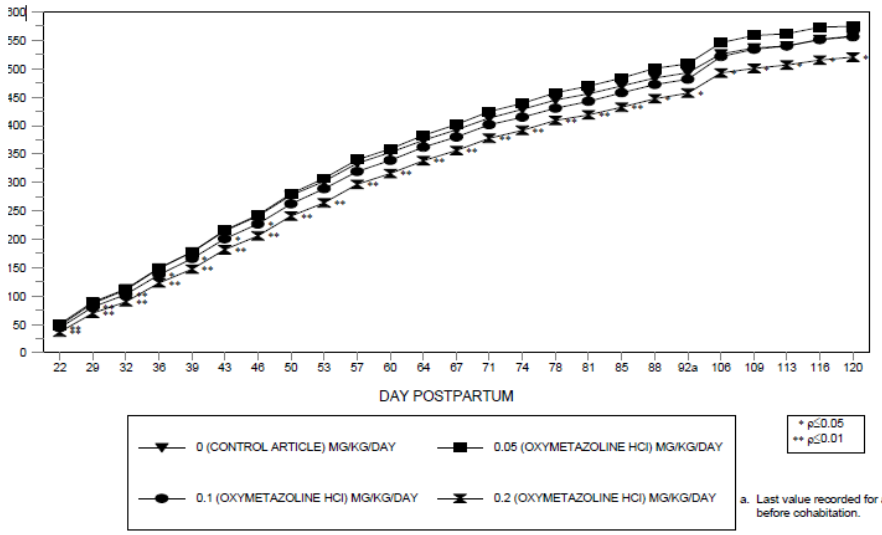
Decreases in body weights were observed at ≥ 0.1 mg/kg/day maternal dose, but they appeared to

be reversible. During the gestation period, average body weights continued to be decreased only in the 0.2 mg/kg/day dose group as compared to control. Average male body weights on Day 120 postpartum were 103%, 100%, and 93% of the control group value in the 0.05, 0.1 and 0.2 mg/kg/day maternal dose groups, respectively. Average female body weights on Day 92 postpartum were 99%, 104%, and 95% of the control group value in the 0.05, 0.1 and 0.2 mg/kg/day maternal dose groups, respectively.

The figures below adapted from the submission showed a summary of these findings.

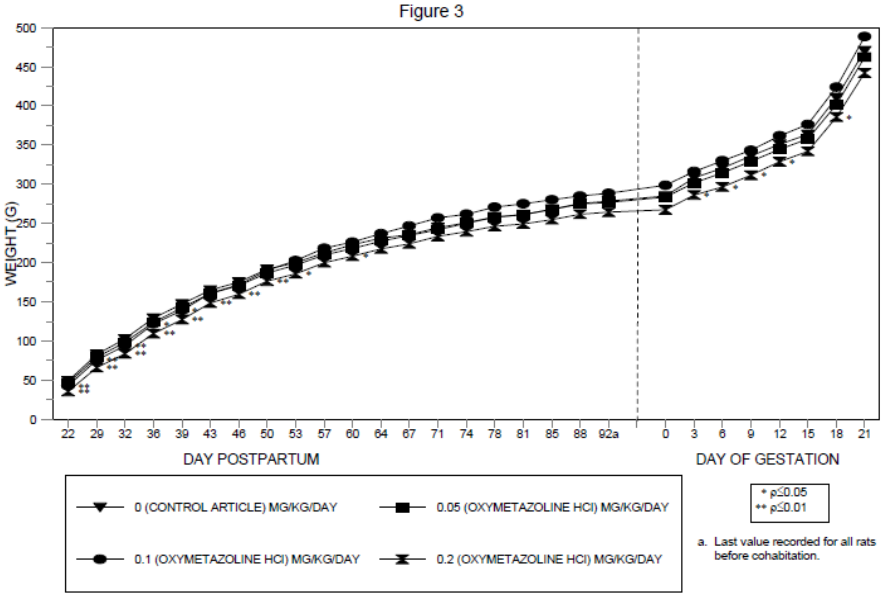
BODY WEIGHTS - F1 GENERATION MALE RATS

Figure 2



BODY WEIGHTS - F1 GENERATION FEMALE RATS

Figure 3



Feed consumption: GD 0, 6, 9, 12, 15, 18 and 21 (female rats)

Transient decreases in absolute food consumption were noted on PPD 43 to 50 and 106 to 113 (6% to 8% below control).

Necropsy observation: On PPD 28 at scheduled euthanasia, one pup in each of the 0.1 and 0.2 mg/kg/day dose groups had slight dilation of the pelvis in the right kidney. One other pup in the 0.2 mg/kg/day dose group had extreme dilation of the third ventricle in the brain and absent eyes. No other necropsy observations occurred.

Prior to PPD 28, totals of 1, 6, 5, and 16 pups were found dead, stillborn, or euthanized in the 0, 0.05, 0.1, and 0.2 mg/kg/day dose groups, respectively. Pups that were autolyzed or partially cannibalized were not necropsied. Necropsy examinations were performed on 1, 3, 4, and 6 F1 pups in the 0, 0.05, 0.1, and 0.2 mg/kg/day dose groups, respectively. One pup in the 0.2 mg/kg/day dose group did not have milk present in the stomach at necropsy.

Terminal weights and Organ weight: Average terminal body weights were slightly decreased (6% below control) in the 0.2 mg/kg/day dose group. No treatment related effects on testes or epididymides weights or the ratios of these weights to the terminal body weight.

The table below showed a summary of these findings.

Body & organ weights:	0 mg/kg/day	0.05 mg/kg/day	0.1 mg/kg/day	0.2 mg/kg/day
Terminal body weight	572	593	572	537
Paired epididymides	1.53 (0.27%)	1.51 (0.26%)	1.53 (0.27%)	1.42 (0.27%)
Paired testes	3.76 (0.66%)	3.78 (0.64%)	3.71 (0.65%)	3.67 (0.69%)

Sexual Maturation: Evaluated from PPD 28 (female) / PPD 39 (males) until the sexual maturation criteria were met. The average days of sexual maturation were delayed for both male and female rats in the 0.1 and 0.2 mg/kg/day maternal dose group. When comparing to the control group, the average postpartum days that the prepuce was observed to be separated in the F1 male rats were delayed by 5% and 10% for the 0.1 and 0.2 mg/kg/day maternal doses group, respectively. When comparing to the control group, the average postpartum days that the vagina was observed to be patent in the F1 female rats was delayed by 3% and 7% for the 0.1 and 0.2 mg/kg/day maternal doses group, respectively.

The results are summarized in the table below.

Sexual maturation:	0 mg/kg/day	0.05 mg/kg/day	0.1 mg/kg/day	0.2 mg/kg/day
Male: preputial separation	45.4±2.2	45.6±2.2	47.6±3.0*	49.8±2.9**
Female: vaginal patency	32.5±1.1	33.2±1.4	33.7±1.9*	34.9±1.9**

* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

Passive Avoidance: Twice from PPD 24 ±1. No treatment related effects were noted in this study.

Watermaze: From PPD 65±5. No treatment related effects were noted in this study.

Mating and Fertility: At PPD 90. No treatment related effects were noted in this study. The results are summarized in table below.

Mating/Fertility:	**0 mg/kg/day**	**0.05 mg/kg/day**	**0.1 mg/kg/day**	**0.2 mg/kg/day**
# in cohabitation (male)	22	22	22	22
Fertility index	20/22 90.9%	22/22 100%	19/22 86.4%	21/22 95.4%
Pregnant	20/22	22/22	19/22	21/22
# in cohabitation (female)	22	22	22	22
Fertility index	20/22 90.9%	22/22 100%	19/22 86.4%	21/22 95.4%
Pregnant	20/22	22/22	19/22	21/22

C-sectioning and litter observations: The average number of corpora lutea was significantly decreased at 0.2 mg/kg/day as compared to control; however the value is within the historical control.

The litter averages for implantations, percent preimplantation loss, litter sizes, live fetuses, early and late resorptions, fetal body weights, percent postimplantation loss, percent dead or resorbed conceptuses, and percent live male fetuses were comparable among the 4 groups and did not significantly differ.

The table below showed a summary of these findings.

C-section data/litter observations:	**0 mg/kg/day**	**0.05 mg/kg/day**	**0.1 mg/kg/day**	**0.2 mg/kg/day**
Rat examined	22	22	22	22
Rats C-sectioned on GD21	20	21	19	21
Implantation	16.3	15.5	17.3	15.2
Litter size	15.6	14.5	16.6	14.8
Resorptions	0.7	1.0	0.6	0.4
Fetal body weights	5.50	5.56	5.46	5.58
Live male/litter	166 54%	154 50%	147 47%	168 54%
Gross examination F2	**0 mg/kg/day**	**0.05 mg/kg/day**	**0.1 mg/kg/day**	**0.2 mg/kg/day**
Litters evaluated	20	20	19	21
Fetuses	312	305	316	311
Thread-like tail	1	0	0	0

F2 Generation

Survival:	No treatment related effects on mortality or clinical signs were noted.
Body weights:	No treatment related effects on body weight were noted.
External evaluation:	No treatment related effects were noted.
Male/Female ratio:	No treatment related effects were noted.

10 Special Toxicology Studies

Phototoxicity test in guinea pigs (Study number: TO9-5661): Under the assay conditions, oxymetazoline HCl cream 2% did not cause any phototoxicity in guinea pigs exposed to UVA (320-400nm) light.

11 Integrated Summary and Safety Evaluation

Oxymetazoline HCl is a synthetic, direct-acting, imidazoline-type alpha1A adrenoceptor agonist. All selective alpha1 agonists are vasoconstrictors, and thus have been used as decongestants to treat allergic rhinitis and conjunctivitis by decreasing erythema and edema of the nasal and ocular mucous membranes, respectively. Oxymetazoline originally developed by E. Merck in Germany in 1961, was approved by FDA in 1964 as a nasal decongestant Drixine®. The drug is also the active ingredient in several over-the-counter drug products to treat allergic rhinitis and conjunctivitis (e.g. Afrin® nasal spray 0.05%, Dristan, Nasivin, Logicin, Vicks Sinex, and Visine L.R. and OcuClear® ophthalmic solution 0.025%).

The toxicity profile of oxymetazoline HCl topical cream has been well characterized by the nonclinical studies conducted by the sponsor.

No evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay); and one in vivo genotoxicity test (rat micronucleus assay at oral doses ≤ 2.5mg/kg/day) was noted for oxymetazoline.

Repeat-dose dermal toxicity studies were conducted in rats for up to 6 months and in minipigs for up to 9 months with oxymetazoline cream. Tail lesions and local toxicities were observed in rats.

The oral Tg.ras H2 mouse assay at doses up to 2.5 mg/kg/day oxymetazoline did not reveal any neoplastic changes. A treatment related increased incidence of non-neoplastic lesions was noted in kidney, brain and mesenteric lymph nodes.

The potential reproductive toxicity was evaluated in an oral fertility study in rats, oral embryofetal development studies in rats and rabbits, a dermal embryofetal development study in rabbits and an oral pre- and post-natal development study in rats. In the rat

oral pre- and post-natal development study, increases in pup mortality was noted at 0.2 mg/kg/day and decreased pup weights, necropsy observations, and delayed sexual maturation was noted at ≥0.1 mg/kg/day. The prenatal and developmental NOAEL was identified as 0.05 mg/kg/day.

No safety issues have been identified for the excipients and impurities during this NDA review.

A comprehensive nonclinical safety profile for RHOFADE supports the safety of the proposed clinical dosing regimen for the topical treatment of persistent facial erythema associated with rosacea. This NDA is approvable from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

Appendix 1: Multiple of human exposure calculations

Human PK data (clinical maximal use PK study conducted with 28 days of once daily application of RHOFADE): mean $AUC_{0\text{-}24\ hr}$ = 1050 pg·hr/mL on Day 28 (per the clinical pharmacology reviewer, Dr. Yanhui Lu)

Reproductive toxicity studies

1) Oral rat embryofetal development study

GD 17 $AUC_{0\text{-}tlast}$ for 0.2 mg/kg/day oxymetazoline HCl dose: 3.43 ng.hr/mL or 3430 pg.hr/mL
GD 17 $AUC_{0\text{-}tlast}$ for 0.1 mg/kg/day oxymetazoline HCl dose: 1.77 ng.hr/mL or 1770 pg.hr/mL

Multiple of human exposure for 0.2 mg/kg/day dose in pregnant rats is 3X (3430 pg.hr/mL ÷ 1050 pg·hr/mL = 3.3)

Multiple of human exposure for 0.1 mg/kg/day dose in pregnant rats is 2X (1770 pg·hr/mL ÷ 1050 pg·hr/mL = 1.7)

2) *Oral rabbit embryofetal development study*

GD 16 $AUC_{0\text{-}24\ hr}$ for 1 mg/kg/day oxymetazoline HCl dose: 76.2 ng.hr/mL or 76200 pg.hr/mL

GD 16 $AUC_{0\text{-}24\ hr}$ for 0.5 mg/kg/day oxymetazoline HCl dose: 28.2 ng.hr/mL or 28200 pg.hr/mL

Multiple of human exposure for 1 mg/kg/day in pregnant rabbits is 73X (76200 pg·h/mL ÷ 1050 pg·hr/mL = 72.6)

Multiple of human exposure for 0.5 mg/kg/day in pregnant rabbits is 27X (28200 pg·h/mL ÷ 1050 pg·hr/mL = 26.9)

3) Oral rat peri- and post-natal development study

GD 17 AUC0-$_{tlast}$ for 0.2 mg/kg/day oxymetazoline HCl dose: 3.43 ng.hr/mL or 3430 pg.hr/mL
GD 17 $AUC_{0\text{-}tlast}$ for 0.1 mg/kg/day oxymetazoline HCl dose: 1.77 ng.hr/mL or 1770 pg.hr/mL
GD 17 $AUC_{0\text{-}tlast}$ for 0.05 mg/kg/day oxymetazoline HCl dose: 0.528 ng.hr/mL or 528 pg.hr/mL

Multiple of human exposure for 0.2 mg/kg/day dose in pregnant rats is 3X (3430 pg.hr/mL ÷ 1050 pg·hr/mL = 3.3)

Multiple of human exposure for 0.1 mg/kg/day dose in pregnant rats is 2X (1770 pg·hr/mL ÷ 1050 pg·hr/mL = 1.7)

Multiple of human exposure for 0.05 mg/kg/day dose in pregnant rats is 0.5X (528 pg·hr/mL ÷ 1050 pg·hr/mL = 0.5)

4) Oral rat fertility study

GD 17 $AUC_{0\text{-}tlast}$ for 0.2 mg/kg/day oxymetazoline HCl dose: 3.43 ng.hr/mL or 3430 pg.hr/mL
GD 17 $AUC_{0\text{-}tlast}$ for 0.1 mg/kg/day oxymetazoline HCl dose: 1.77 ng.hr/mL or 1770 pg.hr/mL

Multiple of human exposure for 0.2 mg/kg/day dose in pregnant rats is 3X (3430 pg.hr/mL ÷ 1050 pg·hr/mL = 3.3)

Multiple of human exposure for 0.1 mg/kg/day dose in pregnant rats is 2X (1770 pg.hr/mL ÷ 1050 pg·hr/mL = 1.7)

Appendix 2: Clean copy of recommended wording for Nonclinical sections of the label

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

RHOFADE™ is an alpha1A adrenoceptor agonist indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

8 USES IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with **RHOFADE™** use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies *[see Data]*. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 3 times and 73 times, (b) (4) *[see Data]*.

Animal Data

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogeneisis (3 times the MRHD on an AUC comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogeneisis (73 times the MRHD on an AUC comparison basis). Maternal toxicity (b) (4)

In a rat perinatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (3 times the MRHD on an AUC comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 and 0.2 mg/kg/day (2 times the MRHD and 3 times the MRHD on an AUC comparison basis, respectively). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (one-half of the MRHD on an AUC comparison basis).

8.2 Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breastmilk production, or to establish the level of oxymetazoline present in human breastmilk postdose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOFADE™ (b) (4) and any potential adverse effects on the breastfed child from RHOFADE™ (b) (4) or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymetazoline is an alpha1A adrenoceptor agonist. Oxymetazoline acts as a vasoconstrictor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oxymetazoline hydrochloride was not associated with an increased incidence of neoplastic or proliferative changes in transgenic mice given oral doses of 0.5, 1.0, or 2.5 mg/kg/day oxymetazoline hydrochloride for 6 months.

Oxymetazoline revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo gentoxicity test (mouse micronucleus assay).

Effects on fertility and early embryonic development were evaluated in rats following oral administration of 0.05, 0.1, or 0.2 mg/kg/day oxymetazoline hydrochloride prior to and during mating and through early pregnancy. Decreased number of corpora lutea and increased post-implantation losses were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis). However, no treatment related effects on fertility or mating parameters were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis).

Appendix 3: Executive CAC meeting minutes

Executive CAC
Date of Meeting: August 23, 2016

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abby Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Barbara Hill, PhD, DDDP, Pharm/Tox Supervisor
Cindy Xinguang Li, PhD, DDDP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 208552
Drug Name: Oxymetazoline hydrochloride (HCl) cream, 1.0%
Sponsor: Allergan, Inc., Irvine, CA

Background: Oxymetazoline HCl is a synthetic, direct-acting, imidazoline-type α adrenoceptor agonist. The sponsor submitted a 505(b)(1) NDA application for oxymetazoline HCl cream, 1.0% indicated for persistent facial erythema associated with rosacea. A 6-month Tg.rasH2 mouse carcinogenicity study was included in the NDA submission.

Tg.rasH2 Mouse Carcinogenicity Study:

Tg.rasH2 mice (25/sex/dose) were administered oxymetazoline HCl at 0 (vehicle control, sterile water), 0.5, 1.0, or 2.5 mg/kg/day by oral gavage once daily for 26 weeks. The dose levels received concurrence by the Executive CAC based on the maximum tolerated dose determined in the 28-day mouse oral dose range finding study. Positive control mice (10/sex) received intraperitoneal injections of 1000 mg/kg/day urethane on days 1, 3 and 5.

No drug related neoplastic lesions were noted in this study. Drug related non-neoplastic lesions were noted in kidney, brain and mesenteric lymph nodes. Positive control mice elicited appropriate neoplastic lesions in this study.

Executive CAC Recommendations and Conclusions:

1. The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
2. The Committee concurred that the study was negative for drug related neoplasms.

Reference ID: 3976602

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\
/Division File, DDDP
/BHill, Supervisor, DDDP
/CLi, Reviewer, DDDP
/DWilliam, PM, DDDP
/ASeifried, OND IO

Reference ID: 3976602

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/s/

ADELE S SEIFRIED
08/24/2016

KAREN L DAVIS BRUNO
08/24/2016

Reference ID: 3976602

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/s/

XINGUANG LI
11/16/2016

BARBARA A HILL
11/16/2016