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APPLICATION NUMBER:

210913Orig1s000

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:	210913
Supporting document/s:	SDN001
Applicant's letter date:	10-16-2017
CDER stamp date:	10-16-2017
Product:	Cequa®
Indication:	Treatment of keratoconjunctivitis sicca
Applicant:	SUN Pharma FZE (Princeton, NJ)
Review Division:	Division of Transplant and Ophthalmology Products
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The subject of this NDA submission is Cequa® (OTX-101), a nanomicellar solution containing 0.09% cyclosporine (CsA) for topical ophthalmic administration to treat keratoconjunctivitis sicca (Dry Eye Syndrome). The Applicant has filed a 505(b)(2) NDA application and relies upon Sandimmune®(NDA 050573) and Neoral® (NDA 050715) for most aspects of systemic safety support, a published literature reference for peri-/post-natal development and fertility and original nonclinical studies conducted by the Applicant to support ocular safety and distribution.

1.2 Brief Discussion of Nonclinical Findings

- Administration of Cequa® resulted in higher intraocular exposure in comparison to a currently marketed formulation of topical ocular cyclosporine (cyclosporine 0.1% ophthalmic suspension), which precluded reliance on this drug to establish ocular safety.
- A pivotal 26-week ocular toxicity study was conducted in rabbits with Cequa (cyclosporine 0.09% ophthalmic solution). Cequa did not produce toxicity at dosing regimens approximately 2-fold higher than the proposed clinical dose, on a per eye basis.
- A bridge to the listed drugs (LDs) was established based on a dose comparison between the Applicant's proposed dosing regimen and the approved maintenance doses for the listed oral drug formulations (Neoral® and Sandimmune®), which provided adequate systemic safety support for this application.
    - Bilateral BID administration of Cequa® would result in a daily dose of (b) (4) µg/eye/day or a total daily dose of (b) (4) µg. It should be noted that the commended daily maintenance doses of Neoral and Sandimmune (~ 10 mg/kg/day; (b) (4) are (b) (4) times higher than the total daily dose of Cequa®; therefore, there are no systemic safety concerns beyond those established for the approved oral formulations.
- A bridge to the published literature used to support nonclinical studies of fertility and peri-/post-natal development (Ryffell, 1983; see below) was established based on a dose comparison between the Applicant's proposed dosing regimen and the NOAEL found in those studies.
    - Bilateral BID administration of Cequa® would result in a daily dose of (b) (4) µg/eye/day or a total daily dose of (b) (4) µg/day ((b) (4) µg/kg in a (b) (4) kg adult). The NOAEL established for fertility and peri-/post-natal development in the published literature is 15 mg/kg [Human Equivalent Dose (HED): (b) (4) µg/kg in a (b) (4) kg adult] resulting in a dose margin of approximately (b) (4)-fold over the HED. The total dose of the cyclosporine following ocular administration of Cequa® is much lower than that of the

NOAEL. As such, reliance on this study for fertility and peri-/post-natal safety support is scientifically appropriate.

1.3 Recommendations

1.3.1 Approvability: Approval recommended.

1.3.3 Labeling

1.3.3.1 Applicant's Proposed Labeling (sections relevant to Pharmacology/Toxicology)

8.1 Pregnancy

Risk Summary

(b) (4) Oral administration of teratogenicity at clinically relevant doses [see Data].

Data

Animal Data

(b) (4) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are approximately (b) (4) and (b) (4) times (b) (4) than the (b) (4) recommended human dose of (b) (4) (b) (4) No (b) (4) of embryofetal (b) (4) observed in rats or rabbits receiving cyclosporine during organogenesis at oral (b) (4) doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. (b) (4) approximately (b) (4) and (b) (4) times (b) (4) than the (b) (4) recommended human ocular dose of (b) (4)

An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. (b) (4) No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (b) (4)

There are no adequate and well-controlled studies of **TRADEMARK™** in pregnant women.

8.2 Lactation

Risk Summary

(b) (4) cyclosporine blood concentrations are (b) (4) low (b) (4) after topical ocular administration of **TRADEMARK™**, [see Clinical Pharmacology (12.3)], (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **TRADEMARK™** and any potential adverse effects on the breast-fed child from cyclosporine.

12.1 Mechanism of Action

(b) (4) Cyclosporine is an immunosuppressive agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, topical administration of cyclosporine (b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The

hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately (b) (4) times (b) (4)

Mutagenesis

Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. (b) (4)

Impairment of Fertility

(b) (4)

1.3.3.2 FDA Proposed Labeling

Applicant's Proposed Text	Reviewer Recommendations
8.1 Pregnancy Risk Summary (b) (4)	**8.1 Pregnancy** Risk Summary There are no adequate and well-controlled studies of Cequa® administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses *[see Animal Data]*.

(b) (4)	
Animal Data (b) (4) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body (b) (4)) are approximately (b) (4) and (b) (4) than the (b) (4) recommended human dose (b) (4) No (b) (4) of embryofetal (b) (4) (b) (4) observed in rats or rabbits receiving cyclosporine during organogenesis at ora (b) (4) doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. (b) (4)	*Animal Data* Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were (b) (4) and (b) (4) times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5µg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively ((b) (4) and (b) (4) times higher than the MRHOD, respectively).
An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. (b) (4) No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (b) (4)	An oral dose of 45 mg/kg/day cyclosporine ((b) (4) times higher than MHROD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day ((b) (4) times higher than the MRHOD).

There are no adequate and well-controlled studies of **TRADEMARK™** in pregnant women.	~~There are no adequate and well-controlled studies of **TRADEMARK™** in pregnant women.~~
8.2 Lactation Risk Summary [redacted] cyclosporine blood concentrations are [redacted] low [redacted] after topical ocular administration of **TRADEMARK™**, [see Clinical Pharmacology (12.3)], [redacted] The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **TRADEMARK™** and any potential adverse effects on the breast-fed child from cyclosporine.	**8.2 Lactation** Risk Summary Cyclosporine blood concentrations are low following topical ocular administration of Cequa® *[see Clinical Pharmacology (12.3)]*. There is no information regarding the presence of Cequa® in human milk following topical administration, the effects on the breastfed infants, or the effects on milk production to inform risk of Cequa® to an infant during lactation. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses *[see Pregnancy (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cequa® and any potential adverse effects on the breast-fed child from cyclosporine.
12.1 Mechanism of Action [redacted] Cyclosporine is an immunosuppressive agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, [redacted]	12.1 Mechanism of Action Cyclosporine is an immunosuppressive agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, topical administration of cyclosporine is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Carcinogenesis Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.	Carcinogenesis Systemic carcinogenicity studies were conducted in male and female mice and rats. In a 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In a 24-month oral (diet) rat study, at doses of 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats (normalized to body surface area) are approximately 55 times higher than the maximum recommended human ophthalmic dose (1.5µg/kg/day), normalized to body surface area.
Mutagenesis Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. (b) (4) [redacted]	Mutagenesis In genetic toxicity tests, cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. Cyclosporine was positive in an *in vitro* sister chromatid exchange (SCE) assay using human lymphocytes.
Impairment of Fertility (b) (4) [redacted]	Impairment of Fertility Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female)

(b) (4)	prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (1620 times higher than the maximum recommended human ophthalmic dose).

2 Drug Information

2.1 Drug

CAS Registry Number: 59865-13-3

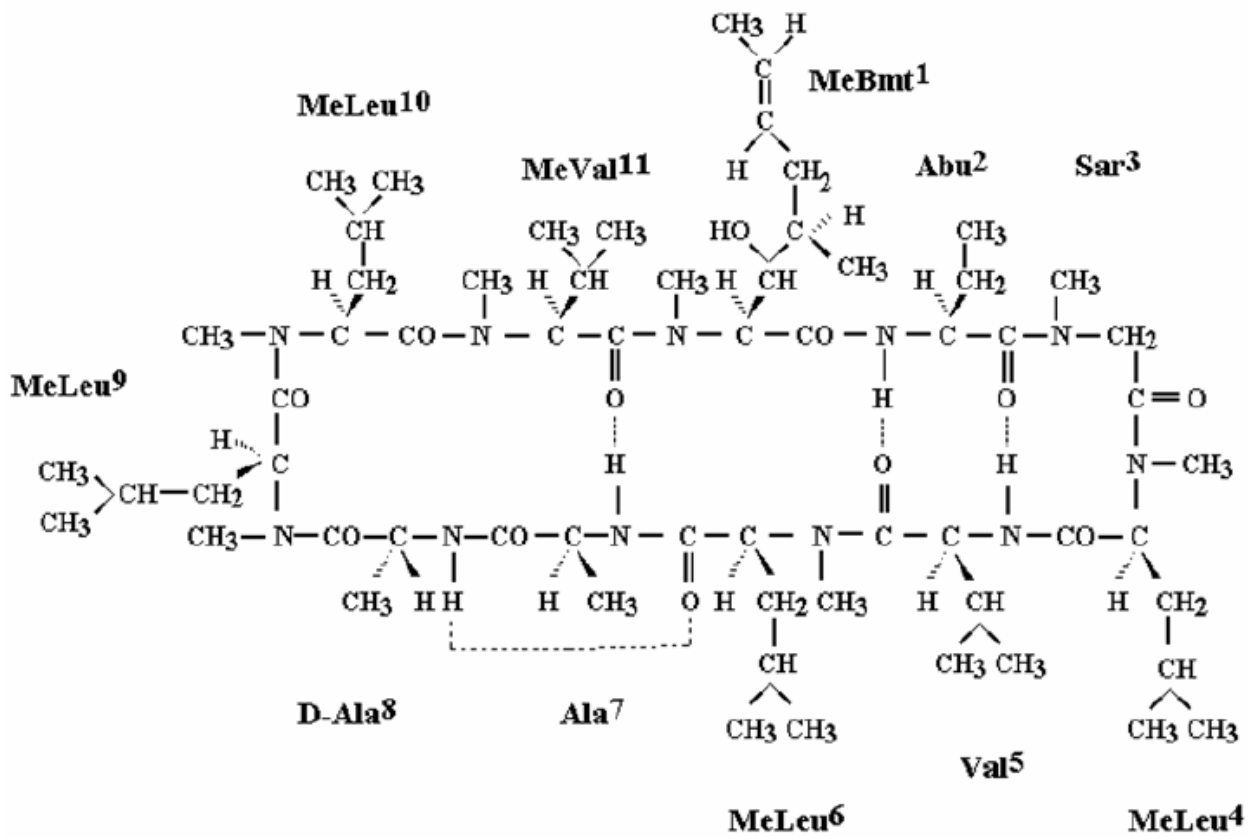
Generic Name: Cyclosporine 0.09% ophthalmic solution

Code Name: Cequa®; OTX-101

Chemical Name: Cyclo-[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

Molecular Formula/Molecular Weight: $C_{62}H_{111}N_{11}O_{12}$ / 1202.6 g/mol

Structure:



Pharmacologic Class: Calcineurin inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

(b) (4)

- IND 118,954 (OTX101)
- NDA 050573 (Sandimmune®; LD on Form 356h)
- NDA 050715 (Neoral®; LD on Form 356h)

(b) (4)

2.3 Drug Formulation

Component	Function	Theoretical Composition per mL	Theoretical Percent Weight per Volume[a]
Cyclosporine, USP[b]	Active Ingredient	(b) (4)	0.09
Polyoxyl (b) (4) Hydrogenated Castor Oil[c], USP/NF		(b) (4)	
Octoxynol-40, (b) (4)			
Sodium Phosphate Monobasic, Dihydrate, USP/NF			
Sodium Phosphate Dibasic Anhydrous, USP/NF			
(b) (4) USP/NF			
Polyvinylpyrrolidone[d], USP/NF			
Hydrochloric Acid (1N) USP/NF			
Sodium Hydroxide (1N) USP/NF			
Water for Injection, USP/NF	Vehicle	(b) (4)	

[a] Rounded to two decimal places
[b] USP/NF=United States Pharmacopeia/National Formulary
(b) (4)

The average drop size is reported as (b) (4) µL.

The Applicant notes that the drug product is a (b) (4) nanomicellar solution (b) (4) It is expected that cyclosporine, due to its hydrophobic character and low aqueous solubility, (b) (4)

2.4 Comments on Novel Excipients

Polyoxyl (b) (4) hydrogenated castor oil is currently qualified to a concentration o (b) (4) % for topical ophthalmic solutions. The Applicant has performed a chronic toxicology study in rabbits (see below) using the clinical formulation and no ocular toxicity was attributed to the vehicle containing polyoxyl (b) (4) hydrogenated castor oil which qualifies the excipient at the proposed concentration of (b) (4) %.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with keratoconjunctivitis sicca (Dry Eye Syndrome)

Instill one drop twice daily (approximately 12 hours apart) into each eye using a single-use container. Can be used concomitantly with artificial tears, allowing a 15-minute interval between products.

Reviewer's note: Bilateral BID administration of Cequa® would result in a daily dose of (b)(4) µg/eye/day, or a total daily dose of (b)(4) µg/2 eyes/day. It should be noted that the recommended daily maintenance doses of Neoral (up to (b)(4) mg/kg/day; (b)(4) mg/day for (b)(4) kg person) and Sandimmune ((b)(4) mg/kg/day; 600 mg/day for 60 kg person) which are greater than 6000-fold higher than the total daily dose of Cequa®, therefore there are no systemic safety concerns beyond those established for the approved oral formulations.

4 Pharmacology

4.1 Primary Pharmacology

Drug class: Calcineurin inhibitor
Mechanism of Action:

(*excerpted from Neoral package insert)*

The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G0- and G1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2.

Reviewer's note: The exact mechanism through which cyclosporine acts to ameliorate signs and symptoms of keratoconjunctivitis sicca (Dry Eye Syndrome) has not been established. The established pharmacologic class of cyclosporine is calcineurin inhibitor immunosuppressant. The mechanism of this mode of immunosuppression acts mainly on T-lymphocytes. Another potential mechanism of cyclosporin A which has been demonstrated in the literature is to block the opening of the mitochondrial permeability transition pore which is associated with preventing cellular apoptosis. Either of these mechanisms may potentiate the amelioration of dry eye sequelae as T-cells and cellular apoptosis have been implicated in the pathogenesis of dry eye disease [reviewed in: Ames, P., and A. Galor, 2015, "Cyclosporine ophthalmic emulsions for the treatment of dry eye: a review of the clinical evidence", *Clin Ivest (Lond.)*, 5(3): 267 – 285.]

4.3 Safety Pharmacology

Systemic exposure, even to the entire intraocular dose at once, is not a significant safety pharmacology concern, given approved LD doses. The Applicant will rely on the systemic safety established for the LD drugs.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

CTD1424: A nanomicellar formulation of cyclosporine (CsA): A single and 7-day repeat dose comparative ocular tissue distribution study of a nanomicellar CsA formulation versus Restasis in New Zealand White rabbits (ITR Study 72372B)

This GLP-compliant study compared the ocular tissue distribution of Cequa (OTX101) versus Restasis® (NDA 050790; not being relied on upon for support of this application) after single or 7-day repeat dosing in female New Zealand White rabbits. Single or repeat dosing consisted of topical ocular instillation of a drop (b) (4) to each eye of the rabbit. In the single dose study, only OTX101 (0.05%) was compared to Restasis whereas in the repeat dose studies, the animals were dosed 4 times daily (2 hour intervals) for 7 days with OTX101 at 0.01, 0.05 or 0.1% concentrations. It should be noted that the approved indicated dosage for Restasis is one drop BID so the single dose phase of this study represents ½x the clinical regimen and the repeat dose phase of this study represents 2x the clinical regimen.

Parameters monitored included daily mortality and clinical signs along with body weight measurements obtained prior to dosing and at termination. Whole blood, tear and ocular tissue samples were collected for CsA analysis from 2 animals per time point. For single dose comparison, sampling time points were 0.25, 0.5, 1, 2, 4, 8, 12, 24, 28 and 72 hours post-dose. Following repeat dose administration, sampling time points were Day 4 (prior to the 1st dose of the day), and Day 7 (prior to the 1st dose of the day, 2 hours after 3rd dose (prior to 4th daily dose), and 0.25, 0.5, 1, 2, 4, 8, and 18 hours after the last (4th) dose administration.

There was no mortality, treatment related clinical signs or changes in body weights attributed to single or repeat dose administration. After a single dose of 0.05% OTX101 ((b) (4) µg CsA/eye), CsA concentrations in the eye were generally higher (1.2 – 2.6-fold) for OTX101 than after administration of Restasis (b) (4) µg CsA/eye), with the exception of the superior eyelid, tears, and vitreous humor. For vitreous humor, all concentrations were below the LLOQ for OTX101. The rank order of exposure was cornea > superior eyelid > tears > third eyelid > superior bulbar conjunctiva > sclera > iris-ciliary body > choroid/retina and lacrimal gland > aqueous humor > lens > whole blood > vitreous humor. The rank order was similar after administration of Restasis except for some variation in the rank order of sample types with closely similar concentrations.

Matrix	Parameter	Restasis (0.05%; (b) (4) µg/eye)	OTX101 (0.05%; (b) (4) µg/eye)	Ratio (AUC_{0-t})
Sclera	C_{max} (ng/g)	29.65	101.95	2.60
	T_{max} (h)	1.00	1.00	
	AUC_{0-t} (h·ng/g)	613.24	1592.93	
Lacrimal gland	C_{max} (ng/g)	17.17	22.08	1.23
	T_{max} (h)	0.50	0.25	
	AUC_{0-t} (h·ng/g)	261.11	321.75	
Aqueous humor	C_{max} (ng/mL)	2.63	6.67	2.17
	T_{max} (h)	48.00	24.00	
	AUC_{0-t} (h·ng/mL)	132.31	287.72	
Vitreous humor	C_{max} (ng/mL)	0.71	0.00	0.00
	T_{max} (h)	0.25	0.00	
	AUC_{0-t} (h·ng/mL)	0.43	0.00	
Superior bulbar conjunctiva	C_{max} (ng/g)	239.15	861.50	1.76
	T_{max} (h)	0.50	1.00	
	AUC_{0-t} (h·ng/g)	2210.21	3890.65	
Cornea	C_{max} (ng/g)	307.25	806.50	2.18
	T_{max} (h)	8.00	8.00	
	AUC_{0-t} (h·ng/g)	12532.3	27324.44	
Superior eyelid	C_{max} (ng/g)	1067.25	569.00	0.30
	T_{max} (h)	4.00	1.00	
	AUC_{0-t} (h·ng/g)	28033.74	8300.12	
Third eyelid	C_{max} (ng/g)	284.5	1199.75	2.03
	T_{max} (h)	1.00	0.25	
	AUC_{0-t} (h·ng/g)	2916.68	5934.75	
Iris-Ciliary Body	C_{max} (ng/g)	9.60	57.48	2.04
	T_{max} (h)	1.00	0.25	
	AUC_{0-t} (h·ng/g)	257.28	524.75	
Tears	C_{max} (ng/g)	3408.84	1637.55	0.26
	T_{max} (h)	0.50	0.25	
	AUC_{0-t} (h·ng/g)	28322.86	7272.77	
Lens	C_{max} (ng/g)	1.02	1.67	1.92
	T_{max} (h)	48.00	24.00	
	AUC_{0-t} (h·ng/g)	44.01	84.28	
Choroid/Retina	C_{max} (ng/g)	19.26	30.93	1.44
	T_{max} (h)	1.00	0.25	
	AUC_{0-t} (h·ng/g)	228.12	327.4	
Whole blood	C_{max} (ng/mL)	0.09	1.44	9.08
	T_{max} (h)	2.00	1.00	
	AUC_{0-t} (h·ng/mL)	0.38	3.48	

After repeat dosing, ocular tissue and whole blood concentrations of CsA increased in a dose-related manner after ocular administration of the 0.01%, 0.05%, and 0.1% OTX101 formulations (doses of (b) (4) and (b) (4) µg CsA/eye/dose, respectively). Ocular tissue and whole blood concentrations of CsA following OTX101 administration were higher than those observed following administration of Restasis at the same dose, except for the lacrimal gland, superior eyelid, and tears.

Matrix	Parameter * (Day 7)	Restasis (0.05%; QID (b) (4) µg/eye/dose)	OTX101(0.01%; QID (b) (4) µg/eye/dose)	OTX101 (0.05%; QID (b) (4) µg/eye/dose)	OTX101(0.1%; QID (b) (4) µg/eye/dose)
Sclera	C_{max} (ng/g)	166.00	93.5	261.25	591.50
	T_{max} (h)	6.25	6.25	6.50	7.00
	AUC_{0-t} (h·ng/g)	1398.01	163.67	2579.41	5010.06
Lacrimal gland	C_{max} (ng/g)	140.73	78.08	63.95	271.20
	T_{max} (h)	6.50	6.50	7.00	8.00
	AUC_{0-t} (h·ng/g)	1002.1	92.10	450.14	1482.79
Aqueous humor	C_{max} (ng/mL)	28.15	13.43	52.10	113.63
	T_{max} (h)	6.5	6.50	6.50	10.00
	AUC_{0-t} (h·ng/mL)	333.63	21.84	786.56	1407.46
Vitreous humor	C_{max} (ng/mL)	0.72	0.14	1.20	2.57
	T_{max} (h)	6.50	6.25	7.00	6.50
	AUC_{0-t} (h·ng/mL)	3.38	0.02	16.39	26.41
Superior bulbar conjunctiva	C_{max} (ng/g)	1462.50	726.25	1467.50	2080.00
	T_{max} (h)	6.25	6.50	6.50	6.25
	AUC_{0-t} (h·ng/g)	5889.67	987.41	6777.59	9679.25
Cornea	C_{max} (ng/g)	3075.00	1542.50	5410.00	8122.50
	T_{max} (h)	6.25	6.50	7.00	6.50
	AUC_{0-t} (h·ng/g)	36010.94	2836.88	72003.13	105639.69

(b) (4)

Matrix	Parameter *	Restasis (0.05%; (b) (4) µg/eye/dose QID)	OTX101(0.01%; (b) (4) µg/eye/dose QID)	OTX101 (0.05%; (b) (4) µg/eye/dose QID)	OTX101(0.1%; (b) (4) µg/eye/dose QID)
Superior eyelid	C_{max} (ng/g)	12795.00	2450.00	6457.50	10517.50
	T_{max} (h)	7.00	6.50	6.50	24.00
	AUC_{0-t} (h·ng/g)	118504.38	2602.16	41092.00	106250.63
Third eyelid	C_{max} (ng/g)	934.00	726.50	2002.50	3460.00
	T_{max} (h)	6.25	6.25	6.25	6.25
	AUC_{0-t} (h·ng/g)	5807.28	916.46	8906.31	17118.25
Iris-Ciliary Body	C_{max} (ng/mL)	69.08	31.67	137.50	390.75
	T_{max} (h)	8.00	6.50	14.00	10.00
	AUC_{0-t} (h·ng/mL)	720.81	51.48	2070.13	3799.03
Tears	C_{max} (ng/mL)	9420.00	3429.18	2452.42	4172.59
	T_{max} (h)	6.00	8.00	6.25	6.50
	AUC_{0-t} (h·ng/mL)	28588.21	3518.18	15649.00	28551.99
Lens	C_{max} (ng/mL)	22.43	11.25	60.73	125.75
	T_{max} (h)	6.25	8.00	24.00	14.00
	AUC_{0-t} (h·ng/mL)	323.58	21.07	984.78	2169.13
Choroid-Retina	C_{max} (ng/mL)	53.83	21.70	67.15	158.00
	T_{max} (h)	7.00	7.00	7.00	7.00
	AUC_{0-t} (h·ng/mL)	431.29	38.51	855.42	1536.41
Whole blood	C_{max} (ng/mL)	0.56	0.33	2.01	6.18
	T_{max} (h)	6.00	6.25	6.50	6.50
	AUC_{0-t} (h·ng/mL)	2.54	0.48	7.62	15.86

There was an increase in exposure [$AUC_{(0-t)}$] with repeat dosing of OTX101 (0.05%) in all ocular tissues between Days 1 and 7, ranging from 1.40-fold in the lacrimal gland to 11.68-fold in the lens, indicating accumulation with repeat dosing. A similar trend was found for Restasis though accumulation in the lens was seen to a lesser degree (7.35-fold).

Matrix	$AUC_{(0-t)}$					
	Restasis (0.05%; (b) (4) µg/eye/dose)			OTX101 (0.05%; (b) (4) µg/eye/dose)		
	Single dose	Repeat dose	Ratio	Single dose	Repeat dose	Ratio
Sclera	613.24	1398.01	2.28	1592.93	2579.41	1.62
Lacrimal gland	261.11	1002.1	3.84	321.71	450.14	1.40
Aqueous humor	132.31	333.63	2.52	287.72	786.56	2.73
Vitreous humor	0.43	3.38	7.86	0.00	16.39	--
Sup. bulbar conjunctiva	2210.21	5889.67	2.66	3890.65	6777.59	1.74
Cornea	12532.3	36010.94	2.87	27324.44	72003.13	2.64
Superior eyelid	28033.74	118504.38	4.23	8300.12	41092.00	4.95
Third eyelid	2916.68	5807.28	1.99	5934.75	8906.31	1.50
Iris-Ciliary Body	257.28	720.81	2.80	524.75	2070.13	3.94
Tears	28322.86	28588.21	1.01	7272.77	15649.00	2.15
Lens	44.01	323.58	7.35	84.28	984.78	11.68
Choroid-Retina	228.12	431.29	1.89	327.40	855.42	2.61
Whole blood	0.38	2.54	6.68	3.48	7.62	2.19

In New Zealand White rabbits, the results of a 7-day comparative pharmacokinetic study showed that at the same CsA concentration and dosing regimen (0.05%; 4 applications/day), intraocular CsA levels (e.g. vitreous humor, lens, iris-ciliary body) were 3- to 5-fold higher

Matrix	OTX-101 to Restasis CsA AUC_{0-t} ratio	
	0.05% OTX-101	0.1% OTX-101
Sclera	1.85	3.58
Lacrimal Gland	0.45	1.48
Aqueous humor	2.36	4.22
Vitreous humor	4.85	7.81
Superior Bulbar conjunctiva	1.15	1.64
Cornea	2.00	2.93
Superior eyelid	0.35	0.9
Third eyelid	1.53	2.95
Iris-ciliary body	2.87	5.27
Tears	0.55	1.00
Lens	3.04	6.70
Choroid/Retina	1.98	3.56
Whole blood	3.00	6.25

These data, therefore, do not establish a nonclinical bridge to Restasis. Accordingly, the Applicant conducted a 26-week ocular toxicity study of Cequa (OTX101) in rabbits, which was sufficient to establish the ocular safety of the product.

Reviewer's note: The systemic exposure to CsA in human subjects was evaluated following bilateral ocular administration of OTX-101 ophthalmic solution (0.09% CsA; (b) (4) µg CsA/day; (b) (4) µg CsA/eye/day) to healthy human volunteers (N=15) twice a day for 7 days, and once on Day 8 (Study OTX-101-2016-003). Most CsA blood concentrations were below the quantitation limit (0.100 ng/mL) of the liquid chromatography tandem mass spectrometry assay. Pharmacokinetic parameters could only be calculated for 4 out of 15 subjects on Day 8. The mean ± SD $AUC_{(0-4)}$ on Day 8 was 0.526 ± 0.059 hr·ng/mL. Exposure was not associated with any measurable pharmacologic or toxic response.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: CsA nanomicellar formulation: A 26-week ocular tolerability and toxicity study followed by a 4-week recovery period in New Zealand White rabbits

Study no.:	72724B (CTD1529)
Study report location:	IND 118,954 SDN035 (12/20/2016)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11-20-2015
GLP compliance:	Yes (signed)
QA statement:	Yes (signed)
Drug, lot #, and % purity:	0.05% CsA; Batch#CSAU-1323-L11; ≥ 99.36% 0.09% CsA: Batch#CSAU-1323-L12; ≥ 99.38%

Key Study Findings

- Minimal to mild unilateral mixed cell infiltrate was noted in the Harderian gland of all CsA treatment groups. The infiltrate was predominantly heterophils accumulating in the interstitial region and alveolar lumen, occasionally mixed with cellular debris. The findings are not considered adverse and relation to human is uncertain since humans lack Harderian glands.

Methods

Doses:	Bilateral; 0.05% and 0.09%
Frequency of dosing:	Vehicle: QID 0.05%: BID or QID ((b) (4) or (b) (4) µg/eye/day, respectively) 0.09%: QID ((b) (4) µg/eye/day)
Route of administration:	Topical ocular drop
Dose volume:	(b) (4) mL/drop
Formulation/Vehicle:	Clinical vehicle (see above)
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	4/sex/group (no treatment) 6/sex/group (including vehicle control)
Age:	2.5 – 3 months
Weight:	2.4 – 3.3 kg (females) 2.4 – 3.1 kg (males)
Satellite groups:	2/sex/group (recovery)
Deviation from study protocol:	None which affected integrity or interpretability

Observations and Results

Mortality (pre-treatment, twice daily)

- No animals died or were sacrificed prior to schedule

Clinical Signs (cage-side: daily; detailed: pre-treatment, once weekly)

- No changes in clinical signs attributed to the test article

Body Weights (pre-treatment, weekly)

- No changes in body weight attributed to the test article

Feed Consumption (pre-treatment, daily)

- No changes in feed consumption attributed to the test article

Ophthalmoscopy [Draize scoring: treatment phase (twice daily); recovery phase (daily); Slit-lamp biomicroscopy (Hackett-McDonald scoring), indirect ophthalmoscopy, tonometry: Week ¾, Week 7, Week 13, Week 20, Week 26 (end of dosing period), Week 30 (end of recovery)]

- Draize scoring
    - No changes were attributed to the test article
- Hackett-McDonald scoring
    - Conjunctival congestion (grade 1)
        - Vehicle control
            - Week 20
            - Week 25
        - Low dose
            - Week 20
            - Week 25
        - Mid-dose
            - Week 20
            - Week 25
        - High-dose
            - Week 20
            - Week 25
- Indirect ophthalmoscopy
    - No changes attributed to the test article
- Tonometry
    - No changes in intraocular pressure attributed to the test article

Electroretinography [pre-treatment, Week 13/14, Week 26 (end of dosing period), Week 30 (end of recovery); photopic)

- No changes in ERG parameters attributed to the test article

Hematology (pre-treatment, Week 26 (end of dosing period), Week 30 (end of recovery)

- No changes in hematology parameters attributed to the test article

Clinical Chemistry

- No changes in clinical chemistry parameters attributed to the test article

Gross Pathology

- No changes in macroscopic observations attributed to the test article

Organ Weights

- Liver weight
    - The mean absolute liver weights, for all females of placebo control and all CsA dosed groups were statistically significantly decreased compared to the non-dosed controls. However, only the body weight relative to liver weight for the placebo and high dose groups achieved statistical significance compared to the non-dosed control groups. This change was not considered to be of toxicological significance due to the large individual variation in the non-dosed group and as the CsA dosed group results were comparable to the placebo controls.
- Prostate weight
    - The mean body weight relative to prostate weight for high-dose males was found to be statistically significantly increased (+47%) compared to the non-dosed controls. Absolute weight of the prostate was increased by 26% but was not statistically significant from control. Gross abnormalities were not observed and histopathology was not evaluated in prostate. As such, the toxicological significance of the weight change cannot be determined.

Histopathology

Adequate Battery: Thymus, mandibular lymph nodes, spleen, sternum/marrow, eyes, optic nerves, third eyelids, Harderian glands, lacrimal glands, superior eyelid with conjunctiva, superior bulbar conjunctiva, extraocular muscles and abnormal findings of all main and recovery animals from all dose groups including non-treated control.

Peer Review: No

Histological Findings:

- Treatment phase
    - Harderian Gland
        - Minimal to mild unilateral mixed cell infiltrate was noted in the Harderian gland of all CsA treatment groups. The infiltrate was predominantly heterophils accumulating in the interstitial region and

alveolar lumen, occasionally mixed with cellular debris. There was no clear difference in the incidence and/or severity of change between rabbits dosed with (b) (4) and (b) (4) µg/eye/day of CsA or between rabbits receiving the daily dose BID or QID.

- Minimal to mild unilateral or bilateral alveolar epithelium atrophy/degeneration with or without concurrent minimal chronic inflammation (interstitial fibrosis, mononuclear infiltrate, alveolar lumen dilatation/distortion) were noted in the Harderian gland and lacrimal gland of all treatment groups. Findings were present in untreated rabbits and vehicle treated rabbits, and were therefore considered spontaneous background findings. The greater incidence and/or severity of these changes in CsA treatment groups, compared to untreated or control/vehicle rabbits, suggest an exacerbation of spontaneous background findings by the test article. There was no clear difference in the incidence and/or severity of change between rabbits dosed with (b) (4) and (b) (4) µg/eye/day of CsA or between rabbits receiving the daily dose BID QID.

Text Table 1 Group Incidence and Severity of Microscopic Changes in Lacrimal and Harderian Glands of Main Rabbits

Tissue/Finding	Sex	Male					Female				
Group		1	2	3	4	5	1	2	3	4	5
Dose (µg/eye/day)		0*	0*			(b) (4)	0*	0*			(b) (4)
Number of Animals		4	6	6	6	6	4	6	6	6	6
Harderian Gland											
Cell Infiltrate, mixed	**Total**	**0**	**0**	**3**	**1**	**2**	**0**	**0**	**2**	**1**	**3**
(unilateral)	minimal	—	—	2	1	2	—	—	1	1	3
	mild	—	—	1	—	—	—	—	1	—	—
Atrophy/degeneration,	**Total**	**0**	**1**	**5**	**3**	**4**	**1**	**1**	**2**	**2**	**3**
epithelium, alveolar	minimal	—	1	4	2	3	1	1	1	2	3
(unilateral, bilateral)	mild	—	—	1	1	1	—	—	1	—	—
Inflammation, chronic	**Total**	**0**	**1**	**3**	**1**	**3**	**0**	**0**	**1**	**0**	**0**
(unilateral, bilateral)	minimal	—	1	3	1	3	—	—	1	—	—
Lacrimal Gland											
Atrophy/degeneration,	**Total**	**0**	**0**	**4**	**2**	**1**	**1**	**0**	**2**	**1**	**1**
epithelium, alveolar	minimal	—	—	2	1	1	1	—	2	1	1
(unilateral)	mild	—	—	2	1	—	—	—	—	—	—
Cell infiltrate, mixed	**Total**	**0**	**0**	**4**	**2**	**1**	**1**	**0**	**2**	**1**	**1**
(unilateral)	minimal	—	—	4	2	1	1	—	2	1	1

*Group 1 received no treatment and Group 2, CsA Placebo, received Control/Vehicle Item only

- Recovery Phase

- There were no microscopic changes related to treatment with the test article, CsA, in recovery rabbits. CsA-related microscopic changes noted previously in the Harderian gland and lacrimal gland of Main Study rabbits recovered following a 4-week recovery period. Microscopic changes were noted sporadically in the Harderian gland of most treatment groups, including untreated rabbits and control/vehicle rabbits and were, therefore, considered within the range of expected spontaneous background findings. Minimal unilateral or bilateral alveolar epithelium atrophy/degeneration with or without concurrent minimal inflammation were noted sporadically in the Harderian gland of most treatment groups.

Text Table 2 Group Incidence and Severity of Microscopic Changes in Harderian Glands of Recovery Rabbits

Tissue/Finding	Sex	Male					Female				
Group		1	2	3	4	5	1	2	3	4	5
Dose (µg/eye/day)		0*	0*			(b) (4)	0*	0*			(b) (4)
Number of Animals		2	2	2	2	2	2	2	2	2	2
Harderian Gland											
Atrophy/degeneration,	**Total**	**2**	**1**	**0**	**2**	**1**	**0**	**0**	**0**	**1**	**1**
epithelium, alveolar	minimal	2	1	—	2	1	—	—	—	1	1
(unilateral, bilateral)											
Inflammation, chronic	**Total**	**1**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**1**	**0**
(unilateral)	minimal	1	1	—	1	—	—	—	—	1	—

*Group 1 received no treatment and Group 2, CsA Placebo, received Control/Vehicle Item only

Toxicokinetics

Parameter*†	(b) (4) µg/eye/day		(b) (4) µg/eye/day		(b) (4) µg/eye/day	
	Males	Females	Males	Females	Males	Females
Day 1						
Cmax (ng/mL)	0.89 ± 0.44 (8)	0.79 ± 0.29 (8)	1.68 ± 0.66 (8)	1.34 ± 0.38 (8)	2.87 ± 0.76 (8)	2.33 ± 0.87 (8)
Tmax (hr)	0.52 (8)	0.53 (8)	0.50 (8)	0.50 (8)	0.50 (8)	0.50 (8)
AUC(0-4) (hr×ng/mL)	2.18 ± 0.99 (8)	2.03 ± 0.67 (8)	4.04 ± 1.44 (8)	2.86 ± 0.50 (8)	6.63 ± 1.67 (8)	4.80 ± 1.81 (8)
Day 182						
Cmax (ng/mL)	0.70 ± 0.18 (8)	0.67 ± 0.10 (8)	1.78 ± 0.54 (8)	1.24 ± 0.24 (8)	3.30 ± 0.98 (8)	2.06 ± 0.67 (8)
Tmax (hr)	0.50 (8)	0.50 (8)	0.50 (8)	0.50 (8)	0.50 (8)	0.50 (8)
AUC(0-4) (hr×ng/mL)	1.88 ± 0.41 (8)	1.79 ± 0.16 (8)	4.78 ± 1.24 (8)	3.16 ± 0.53 (8)	8.52 ± 2.77 (8)	5.20 ± 1.43 (8)

*Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.
†T_{max} is relative to the last dose of the day.

Reviewer comment: The Harderian gland has overlapping functional similarity to the human lacrimal gland in that it lubricates the eye and eyelids. Additionally, it is a site of immune response and osmoregulation, serves as a photoprotective organ, and is a

source of thermoregulatory lipids in animals. The Harderian gland is not present in humans, and toxicologic relevance/significance of the above rabbit findings to the human is uncertain.

Dosing Solution Analysis

- Dose formulations were stable throughout the duration of the study.

7 Genetic Toxicology

The Applicant will rely on the listed drugs for support regarding genotoxicity.

The Neoral® and Sandimmune® labels are similar and state the following:

> *Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.*

8 Carcinogenicity

The Applicant will rely on the listed drugs for support regarding Carcinogenicity. The labeling for each listed drug is similar but differs in some aspects.

Sandimmune® labeling:

> *Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.*

Neoral® Labeling:

> *Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-*

month rat study, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose (6 mg/kg). The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Published reports indicate that co-treatment of hairless mice with UV irradiation and cyclosporine or other immunosuppressive agents shorten the time to skin tumor formation compared to UV irradiation alone.

9 Reproductive and Developmental Toxicology

The Applicant will rely on the listed drugs for support regarding Reproductive and Developmental Toxicology. The labeling for each listed drug is similar but differs in some aspects of language specific to the formulation.

Sandimmune® labeling: *Pregnancy Category C*

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). Sandimmune Oral Solution (cyclosporine oral solution, USP) has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune Oral Solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune Oral Solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women and therefore, Sandimmune (cyclosporine) should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants, the risk of premature birth is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature

labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

A limited number of observations in children exposed to cyclosporine in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

The alcohol content of the Sandimmune formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients)

Neoral labeling:

Pregnancy Category C

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally.) Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardation.

There are no adequate and well-controlled studies in pregnant women therefore, Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants the risk of premature birth is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Pre-term delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%.

Therefore, the risks and benefits of using Neoral during pregnancy should be carefully weighed.

A limited number of observations in children exposed to cyclosporine in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Neoral in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Neoral.

The alcohol content of the Neoral formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients).

Fertility

The Applicant makes the labeling statement:

"Oral administration of cyclosporine to rats for (b) (4) *weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (1620 times higher than the maximum recommended human ophthalmic dose)."*

This statement is supported by the following published article:

- Ryffal, B., *et al*., 1983, "Toxicological evaluation of cyclosporin A", *Arch Toxicol*, 53(2): 107 – 141.
    - Methods:
        - Male Wistar rats (n=15/group) were treated orally for 12 weeks with CS-A in 2% gelatin at doses of 1.5, 5, or 15 mg/kg/day. Female Wistar rats (n=30/group) were treated 2 weeks prior to mating until weaning of their offspring. Controls received 2% gelatin only. Examination of the adult rats included:
            - Clinical observation and mortality
            - Body weight gain
            - Copulation rate
            - Pregnancy rate
            - Pre-coital interval
            - Gestation length
        - Necropsy of the male rats was performed at the end of the drug administration period, whereas half of the females from each group were killed and examined before delivery and the remainder at weaning. Examinations included embryonic development, physical and functional development, survival and fertility of the offspring.

The surviving offspring were sacrificed at the end of the study and necropsied.

- Results:
  - In male F0 rats (sires), Cs-A inhibited body weight gain (up to 9%), induced nephrotoxicity (polyuria and mild chronic nephritis), and divergent incisor teeth due to atrophic gingivitis.
  - In female F0 rats (dams) no adverse effect was found except for dystocia in two dams of the high dose group (45 mg/kg/day).
  - Copulation, pregnancy rates and pregnancy lengths were not significantly affected by Cs-A administration.
  - Cs-A had no significant effects on implantation, embryonic survival, litter size, body weights, or malformations.
  - In single cases, where mother animals were allowed to litter and raise their offspring, a relatively high pre-/perinatal mortality was observed at the 15 mg/kg dose level; the difference to the control value was not, however, statistically significant.
  - Fertility of randomly selected F1 animals and the development of their offspring (F2 generation) were normal.

Results, F_0 females[a]

Dose (mg/kg)	No. of females						Copulation rate (%)		Pregnancy rate (%)	
	Total		Died		Paired					
Controls	15	15	0	0	15	15	100	100	93	73
1.5	15	15	0	0	15	15	100	87	87	85
5	15	15	0	0	15	15	100	93	87	86
15	15	15	0	0	15	15	100	100	80	67

Dose (mg/kg)	Weight gain (%)						Precoital interval (days)		Pregnancy length (days)	
	Before pairing		During pregnancy		During lactation					
Controls	9	8	40	43	–	4	4.3	3.5	–	22.1
1.5	10	8	43	44	–	6	4.2	3.5	–	22.2
5	9	9	44	41	–	9	3.6	4.1	–	22.2
15	11	9	41	42	–	9	5.5	3.0	–	22.2

[a] Left columns: prenatal part/right columns: postnatal part

Reviewer's note: In the proposed labeling statement, the Applicant mistakenly lists the duration of the dosing period in male F0 rats as (b) (4) weeks. According to the published citation, the length of the dosing period was 12 weeks.

Peri-/Post-natal Development

The Applicant makes the following statement:

"An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is (b) (4) *times greater than the cyclosporine in a daily recommended human ocular dose of TRADEMARK™. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (* (b) (4) *times greater than the cyclosporine in a daily recommended human ocular dose of TRADEMARK™)."*

This statement is supported by the following published article:

- Ryffal, B., *et al*., 1983, "Toxicological evaluation of cyclosporin A", *Arch Toxicol*, 53(2): 107 – 141.
    - Methods:
        - Inseminated female Wistar rats (n=24/group) were given CS-A orally at doses of 5, 15, and 45 mg/kg/day from day 15 p.c. until 21 post-partum. Adults were observed for toxic signs and killed at the end of the treatment period. The peri- and postnatal survival, the physical and functional development as well as the fertility and general reproductive performance of the offspring were analyzed.
    - Results:
        - Doses up to 15 mg/kg/day were well tolerated.
        - 45 mg/kg/day
            - Weight gain in dams was reduced (12% lower) at the high dose compared to control animals.
            - An increase of pre-/perinatal mortality (+19.1%) as well as early postnatal mortality (+70.2%) of the offspring compared to controls was observed at high dose.
            - Body weight development of the offspring was markedly inhibited (-18%) compared to controls
            - The incidence of morphological and functional alterations in the offspring of treated animals was not changed compared to the controls.
            - The fertility of randomly selected F1 pups and the development of their offspring (F2 generation) were not significantly not affected.

Results of F_0 females

Dose (mg/kg)	No. of females		weight gain (%) during treatment		Pregnancy rate (%)	Pregnancy length (days)
	Inseminated	Died	Pregnancy[a]	Lactation		
Controls	24	0	16	10	92	22.3
5	24	0	15	13	96	22.1
15	24	0	15	14	92	22.3
45	24	0	4	18	96	22.1

Litter Data

Dose (mg/kg)	Implantations	Litter size (day 0 pp)	Pre- and perinatal loss (%)	Postnatal loss (%)	Body weight day 21 pp (g)[b]	Abnormal pups (4)	Behavior affected pups (%)
Controls	10.5	9.8	7.7	0.9	47.6	4.0	29.2
5	10.8	9.9	8.2	4.9	48.3	1.1	35.8
15	11.0	10.3	7.3	0.0	51.3	0.5	35.4
45	9.2	7.0	26.8*	71.6*	29.5*	0.0	–

Results of F_1 fertility study

Dose (mg/kg)	Copulation rate (%)	Pregnancy rate (%)	Pre- and perinatal loss (%)	Postnatal loss (%)	Abnormal F_2 pups (%)
Controls	100	95	4.0	0.6	0.4
5	100	81	5.2	1.5	1.6
15	95	80	5.1	1.8	0.0
45	100	100	6.0	0.0	0.0

* $p < 0.05$
[a] Days 15–20 p.c.
[b] Combined results of males and females

11 Integrated Summary and Safety Evaluation

Table 1 Safety margins over human clinical dose for toxic effect (LOAEL) and NOAEL doses found in the nonclinical studies

Toxicity	Species	Toxic dose (LOAEL) or NOAEL (no effect)	Safety Margin Based on *
No ocular toxicity (26-week study)	Rabbit	(b) (4) µg/eye/day (high-dose)	1.89-fold
Teratogenicity	Rat	LOAEL: 30 mg/kg/day NOAEL: 17 mg/kg/day	3243-fold 1838-fold
	Rabbit	LOAEL: 100 mg/kg/day NOAEL: 30 mg/kg/day	21622-fold 6486-fold
Postnatal mortality	Rat	LOAEL: 45 mg/kg/day NOAEL: 15 mg/kg/day	4865-fold 1622-fold
Carcinogenesis	Mouse	NOAEL: 1 mg/kg/day	54-fold
	Rat	NOAEL: 0.5 mg/kg/day	54-fold
No Impairment of fertility	Rat	NOAEL: 15 mg/kg/day (high dose)	1622-fold

* Safety margin for ocular safety calculated based on a total dose per eye basis and direct dose comparison to the clinical dose. Systemic safety margins for reproductive toxicology calculated based upon body surface area conversion of the total daily dose administered bilaterally.

Human clinical dose: (b) (4) µg/eye/day; (b) (4) µg/day total daily bilateral dose (b) (4) mg/kg/day or (b) (4) mg/m^2).

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/s/

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08/06/2018

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