

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	203-324
Submission Date:	16 September 2013
Drug Product:	riboflavin ophthalmic solutions (0.12% w/v with 20% or 0% dextran)
Trade Name:	Photrexa® and Photrexa (b) (4)
Sponsor:	Avedro, Inc.
Submission Type:	original NDA
OCP Reviewer:	Gerlie Gieser, PhD
Team Leader:	Philip M. Colangelo, PharmD, PhD

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I. Executive Summary

A. Recommendation

NDA 203-324 has been reviewed by the Clinical Pharmacology review team for Photrexa and Photrexa (b) (4) (riboflavin ophthalmic solutions). From the perspective of Clinical Pharmacology, it is recommended that this NDA be approved, provided that satisfactory agreement is reached between the sponsor and FDA regarding the FDA revisions to the language in the package insert.

B. Phase IV Commitments

None from Clinical Pharmacology.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Riboflavin (Vitamin B2) is an ingredient categorized by FDA to be generally recognized as safe (GRAS). There were no pharmacokinetic studies conducted to determine the actual systemic exposures to riboflavin following topical ocular instillation of the 0.12% riboflavin ophthalmic solutions during one-time corneal collagen crosslinking treatment.

In three UVX clinical trials, the proposed 0.12% (w/v) riboflavin ophthalmic solutions were applied topically into the study eyes of patients with progressive keratoconus or corneal ectasia following refractive surgery. In patients randomized to corneal collagen crosslinking (CCXL) treatment, following removal of the corneal epithelium (b) (4) riboflavin eyedrops were instilled 1 drop every 2 minutes for 30 minutes prior to UVA irradiation and during the 30-minute irradiation period. (b) (4) riboflavin eyedrops were also instilled into the eye if there was inadequate corneal swelling prior to UVA irradiation. Patients assigned to the sham control group also received the riboflavin eyedrops but were not subjected to corneal epithelial debridement and UVA illumination.

Based on the reviewer's analysis, the administration of the (b) (4) riboflavin ophthalmic solution was consistent with the study protocol and the proposed labeling recommendation, whereas the total number of instilled drops of the (b) (4) riboflavin solution was highly variable depending on the attainment of the threshold corneal thickness (at least 400 microns). The systemic exposure to riboflavin during the CCXL treatment of the study eye (following a mean dose < 10 mg, assuming 100% bioavailability of the topically instilled eyedrops) does not exceed that achievable from the oral intake of 35 mg riboflavin (i.e., the World Health Organization's upper limit of riboflavin daily intake for a 70 kg person; oral bioavailability ~100%). None of the patients in the three UVX trials received a topical ocular riboflavin dose exceeding 20 mg over the 12-month study.

During corneal collagen crosslinking treatment, riboflavin acts as a photosensitizer allowing for the enhanced absorption of UV radiation by the corneal collagen fibrils. In the three UVX clinical trials, study participants discontinued consumption of ascorbic acid (vitamin C) dietary sources from one week prior to the day of ocular surgery and until completion of the CCXL treatment procedure with riboflavin (vitamin B2). The potential for interaction between the two vitamins during the UV irradiation phase should be reflected in the US package insert of Photrexa® and Photrexa (b) (4) (riboflavin) ophthalmic solutions.

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RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

II. Question Based Review

A. General Attributes of the Drug

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Riboflavin or vitamin B2, a water soluble vitamin, is an essential nutrient and a natural component of many food products. It is considered to be non-toxic and Generally Recognized as Safe (GRAS).

Two riboflavin 5'-phosphate ophthalmic solutions are proposed for marketing. Photrexa® is a sterile (b) (4) solution containing 0.12% riboflavin (as the active moiety) and 20% dextran. Photrexa (w) (4) is a sterile (b) (4) solution containing 0.12% riboflavin and 0% dextran. In clinical trials, riboflavin ophthalmic solutions with riboflavin concentrations within (b) (4)% of the proposed labeled claim were used.

In addition to riboflavin, Photrexa and Photrexa (b) (4) contains a buffering system consisting of sodium phosphate monobasic and dibasic dihydrate, sterile water for injection as solvent, and sodium hydroxide (b) (4). Photrexa® also contains 20% dextran 500 (b) (4) (w) (4) and sufficient sodium chloride (b) (4) (b) (4).

Both the Photrexa and Photrexa (b) (4) solutions will be supplied in a single-use 3 mL glass syringe equipped with a plunger stopper. The sterile solutions are intended for topical ocular application during corneal collagen crosslinking treatment. The package insert will prominently state that the solutions are not intended for injection.

Table 1 summarizes the physical properties of the riboflavin ophthalmic solutions.

Table 1. Quality Control Tests and Acceptance Criteria for Photrexa and Photrexa (b) (4)

Test Description	Method	Acceptance Criteria
Appearance	Visual	A glass syringe containing a clear, yellow solution, no visible particulates, and no leakage
Identification	RP-HPLC	Retention time (b) (4) and UV spectra conform
Assay	RP-HPLC	(b) (4) % of the label claim
Riboflavin 5'-monophosphate	RP-HPLC	Not less than (b) (4) % Relative Area
pH	USP <791>	(b) (4)
Sterility	USP <71>	No growth
Viscosity	USP <911>	Photrexa: (b) (4) cP Photrexa (b) (4) (w) (4) P
Osmolality	USP <785>	Photrexa: (b) (4) mOsm/kg Photrexa (b) (4) (w) (4) mOsm/kg
Particulate Matter	USP <789>	(b) (4) particles/mL (w) (4) particles/mL particles/mL
Endotoxin	USP <85>	(b) (4) EU/mL
Degradants	RP-HPLC	Specified: (b) (4) NMT numerical value* (b) (4) NMT numerical value* Unspecified: NMT numerical value * Total: NMT numerical value *

*To be established during additional HPLC method validation.

2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Corneal collagen crosslinking (CCXL) using the (b) (4) riboflavin ophthalmic solutions and UVA irradiation is indicated for (b) (4)

Riboflavin is used in CCXL as a photosensitizer, allowing the cornea to absorb a greater amount of the UV irradiation. The oxygen free radicals produced induces the formation of intra- and inter-collagen fibril covalent bonds, leading to biomechanical stabilization of the cornea.

3. What are the proposed dosage(s) and route(s) of administration?

The 0.12% (w/v) riboflavin ophthalmic solutions are for topical ocular administration during the corneal collagen crosslinking (CCXL) treatment of patients with keratoconus or corneal ectasia. The CCXL procedure requires the instillation of Photrexa ((b) (4) riboflavin with 20% dextran) and if needed, Photrexa (b) (4) ((b) (4) riboflavin without dextran) in several phases, and is summarized as follows:

(b) (4)

At the end of the 30 minute soaking period, examine the eye under the slit lamp for the presence of a yellow flare in the anterior chamber. If the yellow flare is not detected, instill 1 drop of Photrexa every 2 minutes for an additional 2 to 3 drops and recheck for the presence of a yellow flare. This process can be repeated as necessary. Once the yellow flare is observed, perform ultrasound pachymetry. If corneal thickness is less than 400 microns as measured (b) (4) instill 2 drops of Photrexa (b) (4) every 5 to 10 seconds until the corneal thickness increases to at least 400 microns. Irradiation should not be performed unless this 400 micron threshold is met.

Irradiate the eye (b) (4) using the KXL System as per the instructions in the KXL manual. During irradiation, continue topical instillation of Photrexa onto the eye every 2 minutes for the 30 minute irradiation period.

4. Was the dosing of the riboflavin ophthalmic solutions in the UVX clinical trials consistent with the study protocol?

Based on the reviewer's analysis of dosing data in all three UVX clinical trials, the total numbers of (b) (4) riboflavin eyedrops received in the Pre-UVA phase and During-UVA phase (mean: 15-16 drops, with 10th to 90th percentile:14-16 drops) were consistent with the study protocol, i.e., 1 drop every 2 minutes for 30 minutes in each treatment phase (Table 2).

Additionally, pre-UVA treatment of the study eyes with the (b) (4) riboflavin solution was necessary for 25% (ectasia) and 31% (keratoconus) in UVX-001, 53% (keratoconus) in UVX-002, and 70% (ectasia) in UVX-003. In patients who received the (b) (4) riboflavin solution in their study eye, the mean \pm sd total numbers of eyedrops were 144 ± 91 (ectasia) and 123 ± 72 (keratoconus) in UVX-001, 60 ± 26 (keratoconus) in UVX-002, and 91 ± 65 (ectasia) in UVX-003.

Based on the sponsor's response to the FDA information request dated 20 December 2013, the actual mean drop sizes of Photrexa® and Photrexa (b) (4) are 28 mL and 34 mL, respectively. Thus, on average, patients treated with the 0.12% (b) (4) riboflavin solution in the study eye in the UVX trials received a total topical ocular riboflavin dose of 1.0 to 1.1 mg, and if treated with the (b) (4) riboflavin solution an additional total topical ocular riboflavin dose of 2.4 to 5.9 mg.

Table 2. Sum of Riboflavin Eyedrops Received by Sham and UVX Study Eyes of Ectasia and Keratoconus Patients in Studies UVX-001, UVX-002, and UVX-003

STUDY (Disease)	TREATMENT OF STUDY EYE	PHASE - Riboflavin solution	SUM OF RIBOFLAVIN EYEDROPS
			Mean ± SD; (range); [10th - 90th percentile]
UVX-001 (Ectasia)	Sham Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (15-16) [16-16]
UVX-001 (Ectasia)	Sham Primary Eye	During UVA - (b) (4)	15 ± 0; (14-16) [15-15]
UVX-001 (Ectasia)	UVX Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (15-16) [16-16]
UVX-001 (Ectasia)	UVX Primary Eye	(b) (4)	144 ± 91; (48-288) [48-288]
UVX-001 (Ectasia)	UVX Primary Eye	During UVA - (b) (4)	15 ± 2; (13-26) [14-15]
UVX-001 (Progressive Keratoconus)	Sham Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (16-17) [16-16]
UVX-001 (Progressive Keratoconus)	Sham Primary Eye	During UVA - (b) (4)	15 ± 0; (14-16) [15-15]
UVX-001 (Progressive Keratoconus)	UVX Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (16-16) [16-16]
UVX-001 (Progressive Keratoconus)	UVX Primary Eye	AC check - (b) (4)	1 ± 0; (1-1) [1-1]
UVX-001 (Progressive Keratoconus)	UVX Primary Eye	(b) (4)	123 ± 72; (48-240) [48-240]
UVX-001 (Progressive Keratoconus)	UVX Primary Eye	During UVA - (b) (4)	15 ± 0; (15-15) [15-15]
UVX-002 (Progressive Keratoconus)	Sham Primary Eye	Pre-UVA - (b) (4)	16 ± 1; (15-22) [16-16]
UVX-002 (Progressive Keratoconus)	Sham Primary Eye	During UVA - (b) (4)	15 ± 1; (15-19) [15-16]
UVX-002 (Progressive Keratoconus)	UVX Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (16-18) [16-16]
UVX-002 (Progressive Keratoconus)	UVX Primary Eye	AC check - (b) (4)	1 ± 0; (1-1) [1-1]
UVX-002 (Progressive Keratoconus)	UVX Primary Eye	(b) (4)	60 ± 26; (24-144) [48-96]
UVX-002 (Progressive Keratoconus)	UVX Primary Eye	During UVA - (b) (4)	15 ± 1; (15-19) [15-16]
UVX-003 (Ectasia)	Sham Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (14-17) [16-16]
UVX-003 (Ectasia)	Sham Primary Eye	During UVA - (b) (4)	15 ± 1; (14-22) [15-16]
UVX-003 (Ectasia)	UVX Primary Eye	Pre-UVA - (b) (4)	16 ± 0; (16-18) [16-16]
UVX-003 (Ectasia)	UVX Primary Eye	(b) (4)	91 ± 65; (24-288) [48-173]
UVX-003 (Ectasia)	UVX Primary Eye	During UVA - (b) (4)	15 ± 1; (14-19) [15-16]

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Three clinical trials were conducted to evaluate the efficacy and safety of the corneal collagen crosslinking treatment with riboflavin ophthalmic solutions and UVA irradiation in the treatment of keratoconus and corneal ectasia patients. Table 3 summarizes the details of Studies UVX-001, UVX-002, and UVX-003. UVX-001 enrolled keratoconus and corneal ectasia patients; UVX-002 and UVX-003 enrolled keratoconus and corneal ectasia patients, respectively.

Table 3. Clinical trials conducted for riboflavin ophthalmic solutions Photrexa® and Photrexa^(b)(4)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	UVX-001	5.3.5.1.1	Long Term; Efficacy and Safety	Randomized sham controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm ²) Single Treatment Ophthalmic	107; (53 drug; 54 sham)	Patients with keratoconus and corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min
Efficacy and Safety	UVX-002	5.3.5.1.2	Long Term; Efficacy and Safety	Randomized sham-controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm ²) Single Treatment Ophthalmic	147; (73 drug; 74 sham)	Patients with keratoconus	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min
Efficacy and Safety	UVX-003	5.3.5.1.3	Long Term; Efficacy and Safety	Randomized sham-controlled	Riboflavin 0.1% solution; UVA light (365 nm; 3 mW/cm ²) Single Treatment Ophthalmic	130; (67 drug; 63 sham)	Patients with corneal ectasia following refractive surgery	Pre-treatment and during irradiation: Riboflavin 0.1% solution 1 drop every two min for 30 min UVA light: 30 min

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Keratoconus and corneal ectasia are characterized by progressive thinning and steepening of the cornea, resulting in loss of the normally round shape of the cornea, corneal optical irregularities and loss of both uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA). Whereas keratoconus is a naturally occurring ocular condition, ectasia is often a complication of refractive (e.g., LASIK) surgery.

In all three clinical trials (UVX-002, UVX-002, and UVX-003), the primary efficacy endpoint was maximum corneal curvature (K_{max}). Study success was defined as a difference of ≥ 1 diopter (D) in the mean change in K_{max} from baseline to Month 12 between the randomized CCXL group and the sham control group.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Note that the systemic exposure to riboflavin (Vitamin B2) was not determined following one-time topical ocular treatment with 0.1-0.12% riboflavin ophthalmic solutions in keratoconus or ectasia patients undergoing corneal collagen crosslinking.

See also QBR section 4.b for the discussion of maximum riboflavin exposure in the UVX trials.

4. Exposure-response:

a. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Note that there was only one dosing regimen of riboflavin ophthalmic solution evaluated for efficacy and safety in the three UVX clinical trials. The study eyes of keratoconus and corneal ectasia patients who received corneal collagen crosslinking procedure with riboflavin ophthalmic solutions and UVA irradiation showed substantial improvements in corneal curvature compared to those patients who were randomized to the sham control group.

Table 4A summarizes the proportion of keratoconus subjects with a ≥ 1 D decrease (i.e., improvement) from baseline in K_{max} (LOCF and observed data) in the ITT population at Months 3 through 12 by randomized study eye and study (UVX-001 [keratoconus only], UVX-002, and the pooled studies). In UVX-001, UVX-002, and the pooled studies, the proportion of keratoconus subjects with a ≥ 1 D decrease (i.e., improvement) from baseline K_{max} was numerically higher in the CCXL group compared with the sham control group between Months 3 and 12.

Table 4B summarizes the proportion of corneal ectasia subjects with a ≥ 1 D decrease (i.e., improvement) from baseline in K_{max} (LOCF and observed data) in the ITT population at Months 3 through 12 by randomized study eye and study (UVX-001 [corneal ectasia only], UVX-003, and the pooled studies). In UVX-001, UVX-003, and the pooled studies, the proportion of corneal ectasia subjects with a ≥ 1 D decrease (i.e., improvement) from baseline K_{max} (LOCF) was numerically higher in the CCXL group compared with the sham control group between Months 3 and 12.

Table 4A. Proportion of Keratoconus Subjects with a ≥ 1 D Decrease (i.e., Improvement) from Baseline in Kmax by Randomized Study Eye in Keratoconus Subjects (ITT Population): UVX-001 (Keratoconus Only), UVX-002, Pooled UVX 001 and UVX-002

Visit	UVX-001		UVX-002		Pooled Studies	
	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
LOCF						
Month 3	13/29 (44.83)	8/29 (27.59)	22/73 (30.14)	15/74 (20.27)	35/102 (34.31)	23/103 (22.33)
Month 6	15/29 (51.72)	9/29 (31.03)	32/73 (43.84)	14/74 (18.92)	47/102 (46.08)	23/103 (22.33)
Month 12	15/29 (51.72)	9/29 (31.03)	37/73 (50.68)	13/74 (17.57)	52/102 (50.98)	22/103 (21.36)
OBSERVED CASE						
Month 3	13/29 (44.83)	8/29 (27.59)	22/67 (32.84)	13/67 (19.40)	35/96 (36.46)	21/96 (21.88)
Month 6	15/28 (53.57)	7/18 (38.89)	32/67 (47.76)	4/21 (19.05)	47/95 (49.47)	11/39 (28.21)
Month 12	9/20 (45.00)	0/0 (0)	36/69 (52.17)	0/2 (0)	45/89 (50.56)	0/2 (0)

Table 4B. Proportion of Corneal Ectasia Subjects with a ≥ 1 D Decrease (i.e., Improvement) from Baseline in Kmax by Randomized Study Eye in Corneal Ectasia Subjects (ITT Population): UVX-001 (Corneal Ectasia Only), UVX-003, Pooled UVX-001 and UVX-003

Visit	UVX-001		UVX-003		Pooled Studies	
	CXL Group	Control Group	CXL Group	Control Group	CXL Group	Control Group
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
LOCF						
Month 3	3/24 (12.50)	1/25 (4.00)	17/63 (26.98)	6/63 (9.52)	20/87 (22.99)	7/88 (7.95)
Month 6	9/24 (37.50)	1/25 (4.00)	17/63 (26.98)	8/63 (12.70)	26/87 (29.89)	9/88 (10.23)
Month 12	10/24 (41.67)	1/25 (4.00)	18/63 (28.57)	7/63 (11.11)	28/87 (32.18)	8/88 (9.09)
OBSERVED CASE						
Month 3	3/23 (13.04)	1/24 (4.17)	16/62 (25.81)	5/61 (8.20)	19/85 (22.35)	6/85 (7.06)
Month 6	9/22 (40.91)	0/13 (0)	16/59 (27.12)	3/19 (15.79)	25/81 (30.86)	3/32 (9.38)
Month 12	10/20 (50.00)	0/0 (0)	15/54 (27.78)	0/2 (0)	25/74 (33.78)	0/2 (0)

b. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Note that there was only one dosing regimen of riboflavin ophthalmic solution evaluated for efficacy and safety in the three UVX clinical trials.

Based on the reviewer’s analysis, the maximum total number of 0.12% riboflavin eyedrops received by an individual patient during participation in Studies UVX-001, UVX-002, or UVX-003 is 477 eyedrops (Table 5), noting that majority of these eyedrops was in the form of the (b) (4) riboflavin solution, and that some patients had bilateral corneal crosslinking treatments, and/or cross-covered between treatment arms. Assuming a drop volume of 34 microliters for both (b) (4) riboflavin solutions, and 100% bioavailability of topically applied riboflavin as eyedrops, the maximum possible total systemic exposure to riboflavin during participation in the 12-month UVX trials was 19.5 mg, which is less than the World Health Organization’s Upper Limit of acceptable daily intake (ADI) of 35 mg for a 70-kg adult. [Based on literature data, the oral bioavailability of riboflavin could be as high as 96%. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) allocated a group acceptable daily intake (ADI) for riboflavin and riboflavin-5'-phosphate of 0–0.5 mg/kg bw/day (expressed as riboflavin).]

The mean (± sd) total number of riboflavin eyedrops received by ectasia patients in UVX-001 and UVX-003 were 70 (± 57) and 125 (± 87), respectively, whereas progressive keratoconus patients in UVX-001 and UVX-002 received 79 (± 65) and 106 (± 57) riboflavin eyedrops, respectively.

Table 5. Sum of riboflavin eyedrops received by individual patient during participation in UVX Study

STUDY (Disease)	SUM OF RIBOFLAVIN EYEDROPS Mean ± SD; (range); [10th - 90th percentile]
UVX-001 (Ectasia)	70 ± 57; (29-318) [31-141]
UVX-001 (Progressive Keratoconus)	79 ± 65; (31-333) [31-163]
UVX-002 (Progressive Keratoconus)	106 ± 57; (30-357) [31-164]
UVX-003 (Ectasia)	125 ± 87; (30-477) [31-222]

Keratoconus. Per the sponsor, non-ocular events account for approximately 10% and 21% of treatment emergent adverse events (TEAEs) reported from baseline to Month 3 in the CCXL and control groups, respectively. Headache and nasopharyngitis were the only non-ocular treatment emergent adverse events reported for at least 2% of subjects in the CCXL group, and occurring at greater frequency in the CCXL group than in the sham control group. Headache was reported for 4 (3.9%) subjects in the CCXL group and no subjects in the control group. Nasopharyngitis was reported for 2 (2.0%) subjects in the CCXL group and 1 (1.0%) subject in the control group.

Corneal ectasia. Per the sponsor, non-ocular events account for approximately 10% and 20% of TEAEs reported from baseline to Month 3 in the CCXL and control groups, respectively. Headache and dizziness were the only non-ocular TEAEs reported for ≥2% of subjects in the CCXL group, and occurring at greater frequency in the CCXL group than in the sham control group. Headache was reported for 7 (7.7%) subjects in the CCXL group and 3 (3.4%) subjects in the control group. Dizziness was reported for 2 (2.2%) subjects in the CXL group and no subjects in the control group. Note that the study eyes of both the CCXL treatment group and the sham control group received riboflavin eyedrops but only those assigned to the CCXL group had the corneal epithelium removed and were illuminated with UVA.

C. *Intrinsic Factors*

1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?**

Since systemic riboflavin concentrations were not measured following topical administration of the riboflavin ophthalmic solutions at the proposed dosing regimen, it is not possible to explore the influence of intrinsic factors on riboflavin pharmacokinetics.

It is important to note that riboflavin is derived from various dietary sources and is categorized as a Generally Recognized as Safe (GRAS) ingredient by FDA. The corneal collagen crosslinking procedure that uses the riboflavin eyedrops with UV irradiation is also a one-time ocular surgical procedure. Even if assuming 100% bioavailability of riboflavin following topical ocular instillation of the proposed 0.12% riboflavin eyedrops, the average systemic exposure to riboflavin during one-time CCXL treatment of one eye in the 12-month UVX trials did not exceed 10 mg, which is below the Joint FAO/WHO Expert Committee on Food Additives upper limit of acceptable oral daily intake of riboflavin (35 mg for a 70 kg person).

2. **What dosage regimen adjustments, if any, are recommended for each of these specific populations? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

Systemic riboflavin exposures are not relevant to the efficacy of the topically administered riboflavin eyedrops for the treatment of keratoconus and corneal ectasia, but may be relevant to systemic safety. However, low systemic exposures to riboflavin are expected following one-time treatment with topically instilled 0.12% riboflavin eyedrops, and riboflavin (a vitamin) is generally regarded as safe or non-toxic. Thus, dosage adjustment recommendations for riboflavin eyedrops should be considered if there are clinically significant subgroup differences in ocular efficacy.

- a) *elderly*

The sponsor proposes (b) (4)

- b) *pediatric patients*

The proposed package insert of Photrexa and Photrexa (b) (4) will state under *Section 8.4 Pediatric Use* (b) (4)

- c) *gender*

Approximately two-thirds of the study participants in the three UVX trials were males.

Based on the sponsor's subgroup analysis (LOCF), both male and female keratoconus patients showed a mean decrease in Kmax ≥ 1.0 D (i.e., improvement) from baseline at Month 12. In ectasia patients, both gender subgroups showed a mean decrease in Kmax ≥ 0.3 D at Month 12 (LOCF), i.e., -0.3 D for males and -1.4 D for females.

Note that gender-based subgroup analysis of systemic safety (i.e., non-ocular adverse events) was not explored for the following reasons: (1) There was a numerically higher overall rate of non-ocular adverse events in the sham control group than in the CCXL group of keratoconus and corneal ectasia patients. (2) Both CCXL group and sham control group study eyes received riboflavin eyedrops, although only eyes randomized to

the CCXL group were subjected to removal of the corneal epithelium and UVA illumination.(3)The number of patients experiencing non-ocular adverse events of interest (e.g., headaches, dizziness, nasopharyngitis) over the 12-month study period following corneal collagen crosslinking treatment was low.

d) *race*

The majority (77%) of the study participants in the three UVX trials were Caucasians; 10% were African-Americans and 3% were Asians.

Based on the sponsor's subgroup analysis (LOCF), both Caucasian and non-Caucasian keratoconus patients showed a mean decrease in Kmax ≥ 1 D (i.e., improvement) from baseline at Month 12. In ectasia patients, the mean decrease in Kmax at Month 12 was comparable for the two racial subgroups (LOCF), i.e., -0.6 D for Caucasians and -0.8 D for non-Caucasians.

A race-based subgroup exploratory analysis of reported non-ocular adverse events in patients who received riboflavin eyedrops was not conducted for the same reasons as provided for gender-based subgroup analysis, as well as the low number of non-Caucasians in the database.

e) *renal/hepatic impairment*

Renal function and hepatic function were not captured in the patient Case Report Forms. However, per the study protocol, renal or hepatic impairment was not part of the exclusion criteria. Dosage adjustment of riboflavin eyedrops in patients with renal or hepatic dysfunction is not deemed necessary.

D. Extrinsic Factors

1. Drug-Drug Interactions: is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

In the three UVX clinical trials, study participants were instructed to discontinue consumption of ascorbic acid (vitamin C) at least 1 week prior to and until the completion of the corneal collagen crosslinking treatment with riboflavin (vitamin B2) ophthalmic solutions and UVA irradiation. Riboflavin can act as a photosensitizer for the oxidative degradation of ascorbic acid; these two vitamins could potentially interact during the UV irradiation phase of CCXL treatment. Literature evidence also suggests that there is potential for enhanced photodegradation of riboflavin and/or ascorbic acid when both vitamins are in aqueous solution at certain pH conditions, and that the two vitamins have overlapping maximum absorption bands in the UV region.

Given that the estimated plasma elimination half-life of ascorbic acid is 10 hours, 1 week is considered an adequate washout period prior to CCXL treatment.

III. Detailed Labeling Recommendations

The reviewer's recommended labeling changes are marked with an underscore (added text) and a strikethrough (deleted text).

HIGHLIGHTS

DOSAGE AND ADMINISTRATION



...

2. DOSAGE AND ADMINISTRATION

Using topical anesthesia, debride the epithelium using standard aseptic technique. Post epithelial debridement, instill 1 drop of Photrexa topically on the eye every 2 minutes for 30 minutes.

At the end of the 30 minute soaking period, examine the eye under the slit lamp for the presence of a yellow flare in the anterior chamber. If the yellow flare is not detected, instill 1 drop of Photrexa every 2 minutes for an additional 2 to 3 drops and recheck for the presence of a yellow flare. This process can be repeated as necessary. Once the yellow flare is observed, perform ultrasound pachymetry. If corneal thickness is less than 400 microns (b) (4) instill 2 drops of Photrexa (b) (4) every 5 to 10 seconds until the corneal thickness increases to at least 400 microns. Irradiation should not be performed unless this 400 micron threshold is met.

Irradiate the eye for 30 minutes at $3\text{mW}/\text{cm}^2$ using the KXL System as per the instructions in the KXL manual. During irradiation, continue topical instillation of Photrexa onto the eye (b) (4) every 2 minutes for the 30 minute irradiation period.

PLEASE REFER TO THE KXL OPERATOR'S MANUAL FOR SPECIFIC DEVICE INSTRUCTIONS.

...



(b) (4)

8. USE IN SPECIFIC POPULATIONS



(b) (4)

8.4. Pediatric Use

The safety and effectiveness of corneal collagen cross-linking has not been established in patients less than 14 years of age.



(b) (4)

8.5. Geriatric Use

No subjects enrolled in the clinical studies were 65 years of age or older. (b) (4)

(b) (4)

...

(b) (4)

...

12. CLINICAL PHARMACOLOGY

(b) (4)

12.1. Mechanism of Action

(b) (4)

(b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

B. Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 203-324	Brand Name	Photrexa & Photrexa- ^(b) /KXL System ⁽⁴⁾
OCP Division (I, II, III, IV, V)	DCPIV	Generic Name	Riboflavin 0.12% solutions/UVA
Medical Division	DTOP	Drug Class	corneal collagen crosslinker
OCP Reviewer	Gerlie Gieser, PhD	Indication(s)	^(b) (4)
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	sterile ophthalmic solutions (eyedrops) for single use (Photrexa and Photrexa ^(b) contains 20% and 0% ⁽⁴⁾ dextran, respectively.)
Pharmacometrics Reviewer	-	Dosing Regimen	Pre-treatment (30-min) and UVA Irradiation (30-min): 1 drop every 2 minutes; additional drops may be instilled before irradiation if needed to ensure penetration of riboflavin into anterior chamber until threshold corneal thickness (≥ 400 microns) is achieved
Date of Submission	16 September 2013	Route of Administration	Topical ocular
Estimated Due Date of OCP Review		Sponsor	Avedro
Medical Division Due Date		Priority Classification	Priority review
PDUFA Due Date	16 March 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	3		
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Vitamin C (ascorbic acid) and its potential sources were prohibited prior to and during the study as it may interfere with UV absorption and activation of riboflavin.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			Dosing regimen evaluated in Phase 3 trials
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	adribo.xpt
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?				Systemic PK following topical ocular application of product was not determined. Such is acceptable to the reviewer given the following: - Systemic absorption is not required for efficacy since the site of application is the site of drug action. - Riboflavin (vitamin B2) is derived from food and dietary supplements and is GRAS. The

					WHO's upper limit of acceptable daily intake (ADI: 0-0.5 mg/kg; 35 mg for 70 kg adult) of this vitamin is not exceeded during typical crosslinking treatment even if 100% systemic absorption is assumed following topical ocular dosing of the TBM formulation. In rodent toxicity studies, the LD ₅₀ is ≥ 1000 mg after IV or IP injection (HED: 80-160 mg/kg).
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

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

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

None.

NOTE: This resubmission addresses the two Clinical Pharmacology information requests (regarding riboflavin dosing/administration and supporting analysis dataset) included in the RTF letter.

Gerlie Gieser, PhD

Reviewing Clinical Pharmacologist

Date

Philip Colangelo, PharmD, PhD

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERLIE GIESER
01/17/2014

PHILIP M COLANGELO
01/17/2014