CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206185Orig1s000

SUMMARY REVIEW

Deputy Division Director and Cross-Discipline Team Leader Review NDA 206185

Date	August 24, 2018
From	Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Deputy Division Director and Cross-Discipline Team Leader Review
NDA #	206185
Applicant	Sun Pharma Global FZE U.S Representative: Sun Pharmaceuticals Industries, Inc.
Date of Submission	5/7/2018
PDUFA Goal Date	11/7/2018
Type of Application	505(b)(2)
Name	Xelpros (latanoprost ophthalmic emulsion) 0.005%
Dosage forms / Strength	Topical ophthalmic emulsion
Proposed Indication(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Regulatory Action:	Approval

1. Introduction

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% was submitted as a 505(b)(2) application referencing the Agency's summary findings for NDA 20-597, Xalatan (latanoprost ophthalmic solution). The proposed indication is the same as that approved for Xalatan, the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Previous action letters for this application cited facilities which were not incompliance with cGMPs. A May 7, 2018, submission to the new drug application served as a complete, class 2 response to the December 19, 2016, action letter. The manufacturing and testing facilities for this NDA are now deemed acceptable and an overall "Approval" recommendation was entered in Panorama by the Office of Process and Facilities (OPF) on 6-26-2018.

Although numerically inferior to Xalatan (latanoprost ophthalmic solution) 0.005%, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product. The decrease in mean intraocular pressure in Xelpros-treated patients of 6-8 mmHg was approximately 0.5 mmHg less than Xalatan treated patients.

There is substantial evidence of safety consisting of an adequate and well controlled study, reference to the Agency's summary findings for NDA 20-597 and supportive evidence from three additional open-label studies which demonstrate that Xelpros dosed once daily in the evening, is safe for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Elevated intraocular pressure is a major risk factor for optic nerve damage, commonly described as glaucoma. This submission contains reference to the Agency's summary findings for Xalatan (latanoprost ophthalmic solution), an adequate and well controlled trial, and open label safety trials which support the safety and efficacy of Xelpros (latanoprost ophthalmic emulsion) 0.005% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. In the randomized, controlled clinical trial of patients with open angle glaucoma or ocular hypertension with mean baseline IOP of 23 - 26 mmHg, the mean IOP-lowering effect of Xelpros administered once daily in the evening was up to 6 - 8 mmHg.

The safety profile of Xelpros (latanoprost ophthalmic emulsion) 0.005% is similar to other marketed topical prostaglandin analogues. Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%), growth of eyelashes (12%) and eyelash thickening (9%).

Xelpros (latanoprost ophthalmic emulsion) 0.005% is expected to have potential benefits which outweigh the potential risks for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension. The risk for using this drug is consistent with the currently marketed prostaglandin analogs.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP).	Decreasing intraocular pressure, measured by applanation tonometry is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues. It is not uncommon to need more than one class of IOP lowering products to control elevated IOP.	This product, if approved, would add to the choice of prostaglandin analogues which reduce elevated IOP.
Benefit	• Reduction in intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for Study CLR_09_12.	In randomized, controlled clinical trials of patients with open angle glaucoma or ocular hypertension with mean baseline IOP of 23 - 26 mmHg, the mean IOP-lowering effect of Xelpros administered once daily in the evening was up to 6 - 8 mmHg.
Risk and Risk Management	• Topical ophthalmic prostaglandin analogues have been used to lower IOP for over twenty years. The risks for using ophthalmic prostaglandin analogues are well established and consistent primarily of actions related directly related to the pharmacologic action of prostaglandins in the eye, including conjunctival hyperemia, increased pigmentation, enhancement of inflammation, and maintenance of eyelashes/hairs in their growth phase.	The safety database contained in this application was consistent with other prostaglandin analogues and established the safety of Xelpros (latanoprost ophthalmic emulsion) 0.005% dosed once daily in the evening.

2. Background

This application received a Complete Response letter dated November 24, 2014. The letter requested that the applicant:

1. Update the NDA submission in all appropriate sections to indicate the correct dosage form of ophthalmic emulsion.
2. Tighten the proposed acceptance limits for [redacted] (b) (4) and the highest unspecified impurity to no more than [redacted] (b) (4) %.
3. Revise the draft prescribing information.
4. Revise the carton and container labeling.
5. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.

An April 9, 2015, submission to the new drug application served as a complete, class 2 response to the November 24, 2014, action letter. This application received a second Complete Response letter dated July 30, 2015. The letter requested that the applicant:

1. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.
2. Revise the draft prescribing information and the carton and container labeling.

A July 28, 2016, submission to the new drug application served as a complete, class 2 response to the July 30, 2015, action letter. This application received a third Complete Response letter dated December 19, 2016. The letter requested that the applicant:

1. Resolve the deficiencies noted during the inspection of the manufacturing facility located in Halol, India.
2. Revise the draft prescribing information and the carton and container labeling.

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	**Trade Name**	**Established Name**
Alpha-2 agonists		
Allergan, Inc.	Alphagan/Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	Metipranolol

Pharmacologic Class/ Applicant	**Trade Name**	**Established Name**
Vistakon	Betimol	Timolol hemihydrate
Aton Pharma	Timoptic	Timolol maleate
Ista	Istalol	Timolol maleate
Aton Pharma	Timoptic XE	Timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	Acetazolamide
Sandoz, Inc.	N/A	Methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	Brinzolamide
Merck	Trusopt	Dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	Pilocarpine hydrochloride gel
Alcon	Isopto Carpine	Pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	Bimatoprost
Pharmacia	Xalatan	Latanoprost
Alcon	Travatan	Travoprost
Alcon	Travatan Z	Travoprost
Merck	Zioptan	Tafluprost
Alcon	Izba	Travoprost
Sympathomimetics		
Allergan	Propine	Dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	Dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	Dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	Brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	Betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	Unoprostone isopropyl

3. CMC

From the Product Quality Review finalized 7/23/18:

NDA 206185 was resubmitted in response to the December 19, 2016, Complete Response on May 7, 2018. NDA 206185, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product, latanoprost ophthalmic emulsion, 0.005%. All information request and review issues have been addressed and there are no pending approvability issues.

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approval" recommendation was entered in Panorama by the Office of Process and Facilities (OPF) on 6-26-2018. NDA 206185 is recommended for approval by the Office of Pharmaceutical Quality.
(OPQ).

Manufacturing Facility Status

Project Overall Manufacturing Facility Statuses

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	6/26/2018	Pending	NDA-206185-ORIG-1-RESUB-29
Withhold	12/16/2016	Complete Response	NDA-206185-ORIG-1-RESUB-22
Withhold	6/17/2015	Complete Response	NDA-206185-ORIG-1-RESUB-18
Withhold	11/13/2014	Complete Response	NDA-206185-ORIG-1

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Association (per 356h)	Alert
Withhold Approval	11/14/2014	NDA-206185-ORIG-1	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		None
Approve Facility	10/7/2014	NDA-206185-ORIG-1	(b) (4)				CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	5/12/2015	NDA-206185-ORIG-1-RESUB-18					CSN NON-STERILE API BY CHEMIC...		None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18					CTL CONTROL TESTING LABORATOR...	PENDING	None
Approve Facility	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3007512695	676162401	110003680	SUN PHARMA ADVANCED RESEARCH COMPANY LIM...	CTL CONTROL TESTING LABORATOR...	ACTIVE	None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	PENDING	None
Withhold Approval	6/17/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		None
No Evaluation Necessary	5/12/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Withhold Approval	12/16/2016	NDA-206185-ORIG-1-RESUB-22	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD	SLQ STERILE LIQUID (EXCLUDE S...		None
Approve Facility	6/26/2018	NDA-206185-ORIG-1-RESUB-29	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES, LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	None

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 10/17/14:

Sun Pharmaceutical Industries, Ltd (SPARC) seeks approval of Latanoprost Ophthalmic Emulsion, 0.005%, which is intended for the same dosage (1 drop QD or 1.5 µg/day) and administration (once daily in the evening) as that of the approved Listed Drug (LD) Xalatan (NDA 20-597), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The new formulation contains an excipient, (b) (4) which has not been previously approved in an ophthalmic product in the United States. SPARC is relying on FDA's prior findings of the efficacy and safety of latanoprost, as summarized in the most current Xalatan labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of (b) (4) these studies included an additional arm(s) using this excipient. Systemic safety of (b) (4) was evaluated in repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 9/30/14:

The proposed SPARC latanoprost formulation differs from Xalatan in several ways: SPARC latanoprost includes (b) (4) as a (b) (4), and potassium sorbate as a preservative. Xalatan contains 0.02% w/v benzalkonium chloride (BKC) as a preservative. The submitted latanoprost product is an emulsion, not a solution. The applicant submitted a request for an *in vivo* bioavailability (BA) or bioequivalence (BE) waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration.

From the Biopharmaceutics Review dated 10/17/14:

Based on 21 CFR § 320.22 (e), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore, the biowaiver request is granted.

The ONDQA-Biopharmaceutics team has reviewed NDA 206185 and its amendments (Seq. 0008 and Seq.0014) submitted on May 23, and July 19, 2014. From the Biopharmaceutics perspective, NDA 206185 Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v is recommended for **APPROVAL.**

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/26/14:

There are no microbiology deficiencies identified. Endotoxin specification of the drug product is (b) (4) EU/mL. The Applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility and pyrogenicity risks to the final drug product. (b) (4)

There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product. The drug product is preserved and adequate preservative effectiveness testing was conducted during development. This testing is also a part of the long-term stability program.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 11/3/14:

Study CLR_09_12 was an adequate, well-controlled study designed with endpoints to evaluate the safety and efficacy of the intended indication, reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Studies CLR_09_13, CLR_08_01 and CLR_10_01 were open-label studies.

Study CLR_09_12 comparing Xelpros (latanoprost ophthalmic emulsion) 0.005% and Xalatan did not establish equivalence with the preplanned clinical endpoint of change from baseline in intraocular pressure. The decrease in mean intraocular pressure in Xelpros-treated patients of 6-8 mmHg was approximately 0.5 mmHg less than Xalatan treated patients. The data obtained from other submitted open-label studies provides supportive information regarding the decrease from baseline in mean intraocular pressure.

Although numerically inferior to Xalatan, the IOP reduction is a clinically significant reduction in IOP and represents a benefit over the potential risks of using the product.

For additional detail, see the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

8. Safety

From the original Medical Officer Reviews dated 11/3/14 and 11/18/14:

The following studies were included in the Integrated Summary of Safety (ISS) for Xelpros (latanoprost ophthalmic emulsion) 0.005%. The safety analysis dataset for the Integrated Safety Summary included all subjects that were included in the safety analyses in each study.

Table 7.1.1 Studies Used to Evaluate Safety

Study Number / Study Phase	Study Design	Treatment Groups (Numbers of Subjects Treated)	Duration of Treatment / Age
Study CLR_08_01 (India) Phase 3	Multicenter, open-label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	SPARC latanoprost (N=53) Xalatan (N=51)	Once daily for 4 weeks Age ≥ 18 years
Study CLR_10_01 (India) Pilot	Multicenter, open-label, randomized, active-controlled, parallel group Visits on Days 0, 28, and 56.	Subjects previously treated with Xalatan were switched over to SPARC latanoprost (N=25 subjects, 46 eyes)	Once daily for 8 weeks Age ≥ 18 years
Study CLR_09_12 (US, IND 102,842) Phase 3	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84	SPARC latanoprost (N=289) Xalatan (N=289)	Once daily for 12 weeks Age ≥ 18 years
Study CLR_09_13 (US, IND 102,842) Phase 3	Multicenter, open-label, non-randomized, uncontrolled, single group assignment. Visits at Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 36.	Single group, all subjects received SPARC latanoprost (open label extension of prior Study CLR_09_12) (N=161)	Once daily for 36 weeks Age ≥ 18 years

Note: SPARC latanoprost 0.005% is the name used by the applicant during product development. SPARC latanoprost 0.005% and Xelpros (latanoprost ophthalmic emulsion) are interchangeable terms.

Four-hundred and forty-eight subjects were exposed to SPARC latanoprost 0.005% ophthalmic emulsion for a mean of 131.2 days.

Treatment-emergent adverse events which occurred in ≥ 5 % of subjects and more frequently in the Xelpros group compared to the Xalatan group were: eye pain (55%), eye discharge (13%),

growth of eyelashes (12%) and eyelash thickening (9%).

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Safety and effectiveness in pediatric patients have not been established.

This application was presented at the Pediatric Regulatory Committee (PeRC) meeting on August 13, 2014. PeRC concurred with the recommendation to waive the assessment of pediatric patients for all pediatric age groups for this indication. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The prevalence and incidence of pediatric glaucoma is very low. The number of pediatric patients is very small and geographically dispersed.

11. Other Relevant Regulatory Issues

See the Clinical Team Leader Memo dated November 20, 2014, from the original NDA review cycle.

See the Clinical Team Leader Memo dated December 16, 2016, from the second NDA review cycle.

12. Labeling

It is recommended that NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% be approved with the following labeling:

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

13. Regulatory Action

NDA 206185, Xelpros (latanoprost ophthalmic emulsion) 0.005% will be approved for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
08/29/2018

WILEY A CHAMBERS
08/29/2018