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APPLICATION NUMBER:

206185Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	206-185
Submission Date(s):	January 31, 2014
Proposed Brand Name	Xelpros ™
Generic Name	Latanoprost
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Sun Pharmaceutical Industries, Ltd.
Submission Type	Original Standard
Formulation; Strength(s)	Latanoprost Ophthalmic (b) (4) 0.005%
Indication	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

SUMMARY

Latanoprost is a prodrug analog of prostaglandin F2α; upon absorption into the cornea, it is converted to the active moiety, latanoprost acid, which has high affinity and selectivity for the FP subtype of prostanoid receptors. Latanoprost is believed to reduce intraocular pressure (IOP) by increasing aqueous humor outflow, thereby reducing the pressure within the eye and reducing the risk of nerve damage and blindness. Xalatan® (latanoprost ophthalmic solution, 0.005%) was FDA-approved for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension in 1996.

The sponsor (Sun Pharmaceutical Industries, Ltd; SPARC) has submitted this current NDA for a different formulation of latanoprost ophthalmic solution 0.005%. The proposed SPARC latanoprost forumulation differs from Xalatan® in two ways: SPARC latanoprost includes (b) (4), and potassium sorbate as a preservative. Xalatan® contains 0.02% w/v benzalkonium chloride (BKC) as a preservative, which is believed to be associated with some toxic effects *in vitro* and inflammatory and toxic ocular effects in in vivo and clinical studies. Thus BKC-free SPARC latanoprost ophthalmic (b) (4) 0.005% may provide a safer alternative to the existing marketed BKC-containing latanoprost products.

In FDA's Filing Communication Letter dated 04/09/2014 for this NDA submission, FDA stated: "*A request to waive the requirement for the submission of evidence measuring the in vivo bioavailability (BA) or bioequivalence (BE) of your proposed product is not included in your NDA. Please submit the BA/BE waiver request with supporting data*."

Subsequently, the sponsor submitted the request for BA/BE waiver, which is acceptable based on the consideration that the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic (b) (4) 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration. In addition, the

efficacy and safety was demonstrated to be similar for subjects treated with Xalatan or SPARC latanoprost in clinical studes CLR_09_12 and CLR_09_13.

In conclusion, no review and no labeling revisions (*with respect to Section 12.3 Pharmacokinetics*) are needed for this NDA from a clinical pharmacology perspective. NDA 206-185 for Latanoprost Ophthalmic (b) (4) 0.005% (Xelpros™) is recommended for approval from a clinical pharmacology perspective.

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Concurrence:

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cc: Division File: NDA 204822; HFD-520 (CSO/ Milstein); HFD-520 (MO/Boyd); HFD-520 (Chambers); HFD-880 (Lazor)

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/s/

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09/30/2014

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09/30/2014