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APPLICATION NUMBER:

202514Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review of NDA 202514
Review #2

Date	January 31, 2012
From	William M. Boyd, M.D.
Subject	Medical Officer Review
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Submissions	January 13, 2012
PDUFA Goal Date	March 13, 2012
Type of Application	505(b)(1)
Name	Zioptan (tafluprost ophthalmic solution) 0.0015%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction

NDA 202514 for Zioptan (tafluprost ophthalmic solution) 0.0015% received a Complete Response Letter dated November 7, 2011, which cited the following deficiency:

> Your NDA does not provide assurance of the sterility of the final drug product. While you have revised your (b) (4) processing validation protocol in your submission of October 27, 2011, (b) (4) (b) (4) filling procedures using this revised validation protocol. In the absence (b) (4) we cannot determine that the product is sterile and safe for use.
>
> To address this deficiency, provide a report describing three consecutive successful (b) (4) processing simulations (b) (4) that you will use for manufacturing the product using the inspection and accounting procedures provided in the revised (b) (4) processing validation protocol submitted in the October 27, 2011 amendment.

Merck submitted an amendment on January 13, 2012, which constituted a Complete Response.

2. Sterility Assurance

From the Product Quality Microbiology Review finalized 1/18/2012:

On 13 January 2011 the applicant filed a Class 1 resubmission with the requested data from 3 consecutive (b) (4) processing simulations (b) (4) using the revised validation protocol submitted to the agency on 27 October 2011. (b) (4) batches 10019, 10020, and 10021 were manufactured separately and batch 10019 had a sterile (b) (4)

(b) (4). A summary of the three (b) (4) is provided in Table 1 below.

Table 1- Summary results from (b) (4) processing simulation studies (Sponsor Table 3.2.P.3.5-2452-ophsln:11)

Batch Number	Mfg. Date	(b) (4)	# of Units Positive for Growth
10019	20Nov2011		0
10020	22Nov2011		0
10021	24Nov2011		0

The revised (b) (4) procedures were summarized in Module 3.5.5.2 and were consistent with data reviewed for the Product Quality Microbiology Reviews #1 and #2. Briefly, (b) (4) ampules were filled (b) (4) Growth promotion studies are conducted for each batch and must be acceptable.

This application is recommended for approval on the basis of product quality microbiology.

3. Safety Update

Per Merck, the safety data presented in the Safety Update in the January 13, 2012, resubmission, are consistent with those submitted to the original NDA and the Safety Update in May 2011. Therefore, Merck is not proposing any changes to the proposed package insert and proposed patient package insert previously submitted to the FDA.

Currently, there are no ongoing clinical studies for tafluprost that are sponsored by Merck in the US or in any ex-US country. However, there are **two** ongoing ex-US/non- IND, post-marketing surveillance studies for tafluprost that are being sponsored by Merck's development partner, Santen, in some of the countries where they hold the Marketing Authorization.

(b) (4) There were no non-clinical studies that were either ongoing or completed during the reporting period for this Safety Update. The eight ongoing ex-US clinical studies mentioned above are discussed in this Safety Update Report. (b) (4)

Five of these ongoing [(b) (4)] studies are double masked. The sixth study is an open labeled long term safety study for the [(b) (4)] in Japan that has approximately 42 patients exposed to tafluprost monotherapy during the four week open label randomization phase. The remaining two ongoing studies are post-marketing safety surveillance studies for tafluprost in Japan and Korea. In addition to these eight ongoing studies, the final Clinical Study Report of **one** completed study [(b) (4)] study) is being submitted in this Safety Update.

Table 2.7.4: 1

Ongoing Studies to be Included in the Safety Update Report for Tafluprost

Protocol	Study Name	Duration	Treatment Arms and Randomization or Enrollment Ratio	Randomized or Entered N	Status
ONGOING STUDIES					
[(b) (4)] EU Superiority study [(b) (4)]	Phase III, randomized, double-masked study to compare efficacy and safety of the PF [(b) (4)] to tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies	6 months –primary evaluation of efficacy at 3 months; data beyond 3 months used to investigate long-term safety of the [(b) (4)]	Approximately 600 patients will be enrolled to this study: 220 patients (110/group) for the comparison of timolol [(b) (4)] (stratum 1) and 380 patients (190/group) for the comparison of tafluprost [(b) (4)] (stratum 2).	247 currently enrolled	Treatment Phase ongoing
[(b) (4)] EU Non-inferiority study [(b) (4)]	Phase III, randomized, double-masked study to compare efficacy and safety of the PF [(b) (4)] to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly	6 months treatment (up to 4 week washout, 6 months treatment, 1-3 week post-study follow-up).	Approximately 380 patients will be enrolled to this study in 1:1 [(b) (4)] vs concomitant taf and tim	401 currently enrolled	Treatment Phase ongoing
[(b) (4)] EU PK study [(b) (4)]	Ph I , single center, double-masked, 3-period crossover for PK, safety, and tolerability of [(b) (4)] vs PF taf and PF tim monotherapy	Duration of the first, second and third treatment period are 7 days each (Day 1 to Day 7); 4 weeks between the treatment Periods; post-study follow-up period of 1-3 weeks.	15 healthy volunteers will be randomized to ensure that at least 12 healthy volunteers randomized	15 Final Enrollment	Treatment Phase ongoing

Ongoing Studies to be Included in the Safety Update Report for Tafluprost (Cont.)

Protocol	Study Name	Duration	Treatment Arms and Randomization or Enrollment Ratio	Randomized or Entered N	Status
(b) (4) Japan (b) (4)- Taf-Taf/Tim	Phase III Double-masked comparative study (b) (4) compared to Taf monotherapy and Taf/Tim given concomitantly	4 week observation with Taf and 4 week double-masked treatment period	Approx 480 subjects.160 subjects per group in 1:1:1 randomization to (b) (4) (b) (4) or Taf/Tim concomitant administration	374 currently enrolled	Treatment Phase ongoing
(b) (4) Japan (b) (4) Tim	Phase III Double-masked comparative study (b) (4) compared to Timolol monotherapy in patients	4 week observation with tim and 4 week double-masked treatment period	Approx 140 subjects (70 subjects per group) in 1:1 randomization to Tim or (b) (4)	138 currently enrolled	Treatment Phase ongoing
(b) (4) Japan Long Term Safety Study- (b) (4)	Phase III Long term Open Label study of (b) (4)	4 week open randomization; 52 week open label treatment period	Approx 126 subjects (42 subjects per group for each observation period ophthalmic solution); 4 week open label period of pts randomized to Taf, Tim, or Taf/Tim concomitant administration; 52 wk treatment period of patients (b) (4)	136 currently enrolled	Treatment Phase ongoing
Post-approval regulatory commitment, open label study in Japan	TAPROS ophthalmic solution 0.0015% Special Drug Use-results Survey (Investigation on Long-term Use)	Followed for 2, 12 and 24 months, follow-up of 6 months if discontinued TAPROS due to AE	All patients enrolled to tafluprost PC by centralized registration system (TAPROS is the marketed tafluprost in Japan).	4502 tafluprost PC	Treatment Phase ongoing
Post-approval regulatory commitment, open label study in Korea	Post Marketing Surveillance on Safety and Efficacy of Tafluprost PC Eye Drops in Korean Patients in Accordance with "Regulation for Re-Examination of New Drugs, Etc."	Visit for assessment at Week 4; total study duration 6 years after product release.	3000 or more Korean pts.	550 tafluprost PC	Treatment Phase ongoing
(b) (4)					

Taf = PF tafluprost 0.0015% (or PC tafluprost 0.0015% for Japan Studies)
Tim = PF timolol 0.5% (or PC timolol 0.5% for Japan Studies)

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