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RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action #2

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Summary Review
NDA Number	NDA 202514
Related IND	IND 62,690 (MK-2452)
Applicant Name	Merck Sharpe & Dohme Corp. (Merck)
Application Type	505(b)(1)
Date of Original Submission	January 7, 2011 (standard review)
Complete Response Letter	November 7, 2011
Resubmission	January 13, 2012
Amendment - labeling	January 23, 2012
PDUFA Goal Date	March 13, 2012
Proprietary Name / Established (USAN) Name	Zioptan™ Tafluprost ophthalmic solution
Dosage Form	Sterile ophthalmic solution
Dosage Strength	0.0015% (15 micrograms/mL)
Preservative	Preservative free
Route of Administration	Topical
Dose	One drop in affected eye or eyes once daily in the evening
Proposed Indication(s)	reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
How Supplied	Foil pouch containing strip of 10 single-use LDPE ampoule, containing 0.3 mL clear solution
Recommended Action	<i>Approval</i>

Material Reviewed/Consulted for this resubmission	Names of discipline reviewers
Medical Officer (Labeling & Safety Update) Review	Bill Boyd, Wiley Chambers 2/1/2012
CDTL Review	Bill Boyd, Wiley Chambers 2/1/2012
Deputy Director Review	Wiley Chambers, 2/1/2021
Product Quality Microbiology Review	Jessica Cole, John Metcalfe 1/18/2012
Product Quality ONDQA Review	Maotang Zhou, Rapti Madurawe 1/31/2012
DMEPA – Proprietary Name	Jung Lee, Carol Holquist 2/9/2012

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Table of Contents:

Table of Contents:.....	2
1. Summary and Recommendations	3
1.1 Deficiencies:	3
1.2 Post-Marketing Studies:.....	3
1.3 Other Issues.....	3
2. Background	3
3. CMC/Product Quality Microbiology	4
3.1 Product Quality Microbiology Sterility Deficiencies:	4
4. Nonclinical Pharmacology/Toxicology	5
5. Clinical Pharmacology/Biopharmaceutics.....	5
6. Clinical Microbiology/Immunology	5
7. Clinical/Statistical-Efficacy	5
8. Safety	5
9. Advisory Committee Meeting	6
10. Pediatrics	7
11. Other Relevant Regulatory Issues	7
12. Labeling.....	7
13. Decision/Action/Risk Benefit Assessment.....	8
13.1 Regulatory Action.....	8
13.2 Risk Benefit Assessment.....	8
13.3 Recommendation for Postmarketing Requirements (PMR) and Commitments (PMC)	8

1. Summary and Recommendations

Based on the review of the January 13, 2012, resubmission of NDA 202514, the applicant has addressed the manufacturing deficiencies outlined in the *Complete Response* letter dated November 7, 2011, submitted a safety update and resubmitted labeling including a new statement in the package insert that the date when the foil package is opened should be written on the package. Therefore, I agree with the reviewers that the application should be issued an *Approval* letter.

For a complete summary of the findings during the previous review cycle and this review cycle, the Action package, including primary, secondary and tertiary reviews should be consulted.

This review briefly summarizes the information in the January 13, 2012, resubmission and review team recommendations.

1.1 Deficiencies:

None (b) (4) deficiency resolved in this resubmission)

1.2 Post-Marketing Studies:

None

1.3 Other Issues

None

2. Background

Zioptan (tafluprost ophthalmic solution) 0.0015% is a prostaglandin F2 α analogue indicated for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension in adult patients. The dosing regimen is 1 drop of tafluprost solution in the conjunctival sac given once daily in the evening in the affected eye or eyes. The product to-be-marketed is a preservative free (PF), sterile, clear solution supplied in single-dose ampules. Phase 3 clinical trials included both the PF and preservative-containing (PC) formulations; the preservative is benzalkonium chloride. The efficacy of this new molecular entity was demonstrated in two Phase 3 clinical trials (Study 15-003 and 001) conducted in the US and Europe comparing tafluprost to timolol, along with a bridging trial (Study 77550) comparing the PF and preservative-containing formulations. Other Phase 1, 2 and 3 studies conducted during development were also included in the application.

A *Complete Response* letter was issued November 7, 2011, because the application did not provide adequate assurance of sterility of the final drug product. To address this deficiency, the applicant has performed three consecutive (b) (4) runs consistent with the recommendations in the (b) (4)



The applicant conducted this testing in collaboration with (b) (4) and submitted results of the testing on January 13, 2012. A class 1 resubmission was requested and granted.

3. CMC/Product Quality Microbiology

3.1 Product Quality Microbiology Sterility Deficiencies:

The November 7, 2012, *Complete Response* letter stated that the “NDA does not provide assurance of the sterility of the final drug product,” and further noted that although Merck had revised the (b) (4) processing validation protocol in the NDA submission of October 27, 2011, (b) (4) filling procedures using this revised validation protocol. Without the (b) (4) results, FDA cannot determine that the product is sterile and safe for use.

To address this deficiency, Merck was asked to provide a report describing three consecutive successful (b) (4) processing simulations (b) (4) that will be used to manufacture the product using the inspection and accounting procedures provided in the revised (b) (4) processing validation protocol submitted in the October 27, 2011, amendment.

The January 13, 2012, resubmission included the results of the 3 (b) (4) simulating (b) (4) processing, batches 10019, 10020 and 10021, which are summarized in the table below from Dr Cole’s review. The acceptance criteria (b) (4) all units tested were negative. Dr. Cole concluded that the results are acceptable

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

In his Deputy Director Review, Dr. Chambers writes that he disagreed with the requirement for the company to conduct the three (b) (4) requested because it does not appear to be one

of the reasons to not approve an application listed in 21 CFR 314.125. However Dr. Hussong, Associate Director for New Drug Microbiology, our experts in the area of Product Quality Microbiology and Sterility in OPS, wrote in his review that complete validation of the (b) (4) processing is critical to sterility assurance. Per 21 CFR 200.50, ophthalmic products are required to be sterile. Therefore the applicant was asked to address the outstanding deficiency of inadequate assurance of sterility of the final drug product in the November 7, 2011, Complete Response letter. This issue was discussed in detail prior to the final action and is also discussed in the Division Director's Review and the Office Director's Memorandum.

Comment:

Given that ophthalmic products are required to be sterile, (b) (4) are necessary to validate the (b) (4) processing to ensure sterility of the drug product, I agree with Dr. Hussong's recommendation (b) (4) be available before approval for tafluprost, which is incidentally a preservative-free product. Merck has conducted and submitted the 3 (b) (4). This information provides adequate assurance of sterility for the final drug product. The application is now recommended for approval from the Product Quality, including Quality Microbiology, perspective.

4. Nonclinical Pharmacology/Toxicology

No new information submitted

5. Clinical Pharmacology/Biopharmaceutics

No new information submitted

6. Clinical Microbiology/Immunology

Not applicable.

7. Clinical/Statistical-Efficacy

No new information submitted

8. Safety

The November 7, 2011, *Complete Response* letter requested that Merck submit a Safety Update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

In response to the request for a safety update, Merck noted that :

There are no ongoing or completed studies that were sponsored by Merck during the reporting period for this SUR (March 2, 2011 to November 7, 2011).

Safety data from a total of 6 new studies sponsored by our development partner,

(b) (4)
In addition, safety data from 2 ongoing post-marketing safety surveillance studies sponsored by

Santen for preservative containing tafluprost in Japan and Korea are also included. Lastly, the final Clinical Study Report for the (b) (4) study for tafluprost that was not available for submission in the previous SUR in May 2011 is being submitted in this SUR. It should be noted that the safety data from this study were previously discussed in detail and submitted in the May 2011 SUR. The Safety Update Report (SUR) is being submitted in accordance with Merck's SUR proposal submitted to the FDA on December 7, 2011. There were no non-clinical studies that were either ongoing or completed during the reporting period for this SUR."

Merck further notes that of the nine studies, five studies are ongoing double masked studies (b) (4) of tafluprost and timolol. Two of the remaining studies are ongoing open labeled, observational, post marketing, safety surveillance studies for tafluprost, while one is an open labeled long term safety study (b) (4) with approximately 42 patients exposed to tafluprost monotherapy for 4 weeks during the open labeled randomization phase. The remaining study (b) (4) study for tafluprost) was previously discussed in detail in the May 2011 SUR and the safety data were previously submitted to the FDA. Only the final Clinical Study Report for the (b) (4) study that was not available for submission in May 2011 is being submitted in this SUR.

The information in the Safety Update Report (SUR) was reviewed by Dr. Boyd whose review includes a tabular presentation of the studies mentioned above as well as brief summaries of the available information from these ongoing studies. Based on his assessment of the information provided from the studies, he agrees that the findings are comparable to those seen in the original NDA and first safety update. No further labeling recommendations are needed based on the information included in the safety update.

Comment:

The adverse events reported in the safety update for this resubmission do not identify new safety signals and the no labeling revisions are needed based on the information from the safety update. The application is recommended for approval.

9. Advisory Committee Meeting

ZIOPTAN was not referred to an FDA advisory committee because it is a member of the class of ophthalmic prostaglandin analogs with similar potential risks and benefits as other members in this class. The benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee on December 8, 1995, and the safety profile of tafluprost did not raise any new significant safety issues. The clinical design including endpoints of the adequate and well-controlled studies was similar to other approved drugs in this class and we are not aware of any controversial issues that would benefit from further advisory committee discussion.

10. Pediatrics

A waiver was granted during previous review cycle for this indication, because necessary studies are impossible or highly impracticable to conduct as there are too few children with this disease/condition to study.

11. Other Relevant Regulatory Issues

No new information submitted

12. Labeling

The package insert, patient package insert, and carton and container labeling were reviewed as applicable by the Division, DMEPA, DDMAC and the patient labeling group (now part of the Office of Medical Policy). The carton and container labels sent November 4, 2011, and the package insert and patient package insert sent January 23, 2012, incorporate all the requested revisions and are acceptable for approval.

- **Package insert (PI):** The PI is written in PLR format and has been reviewed by all groups, and includes the recommendations made by these groups. DMEPA recommended deleting language that the single-use ampoule is sufficient to treat both eyes to avoid inappropriate use and saving the opened ampoule for future doses and risking bacterial contamination. A statement “discard unused portion” is recommended for this product containing no preservative. Additional comments regarding formatting and font size, bolding, color, and graphics were made. DDMAC’s comments were also incorporated.

Under Section 16 How Supplied/Storage and Handling, the following sentence was added, “Write down the date you open the foil pouch in the space provided on the pouch. Discard any unused containers 28 days after first opening the pouch.”

Comment:

This language is acceptable and needed in the PI because Merck and OMP agreed that language telling patients to write the date they open the package is appropriate and should be in the patient package insert. Therefore, this information also needs to be included in the PI, which includes the statement, “Write down the date you open the foil pouch in the space provided on the pouch” under Instructions for Use to the patient and “Write down the date the pouch is opened here: _____” on the pouch itself. Of note, similar language was included by Merck for Cosopt PF, a dorzolamide/timolol fixed combination product, for reduction of IOP approved on February 1, 2012.

- **Patient package Insert (PPI):** The PI is submitted with the original application was revised to remove promotional, incorrect and misleading language, reviewed by OMP patient package labeling group and DDMAC.
- **Carton and Container Labels:** The labels were reviewed by CMC and DMEPA.

Merck submitted carton and container labels on November 4, 2011, for the commercial presentation for 30 single-use containers (packaged as 3 pouches x 10 single-use containers), and a commercial presentation for 90 single-use containers (packaged as 9 pouches x 10 single-use containers), as well as a professional sample containing one pouch x 10 single-use containers.

- **Proprietary Name:** The applicant's initial proposed proprietary name of Saflutan was unacceptable because of its similarity to Xalatan and the applicant was sent a letter on April 15, 2011. The subsequent proposed proprietary name Zioptan was reviewed and found acceptable from the safety and promotional perspective by DMEPA on August 31, 2011, and a letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on October 31, 2011. The proposed proprietary name was re-reviewed following this re-submission and found to be acceptable on February 9, 2012.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The application is recommended for Approval as the deficiency from the *Complete Response* letter of November 7, 2011 have been addressed.

13.2 Risk Benefit Assessment

As noted in prior reviews from the original review cycle, two Phase 3 studies demonstrated that Zioptan is effective in the reduction of IOP in patients with open-angle glaucoma and ocular hypertension, by meeting their pre-specified NI margin, and a bridging study demonstrated that the PC and PF formulations had similar efficacy.

The safety profile of tafluprost is consistent with the adverse reactions previously identified for this class including pigmentary changes and some ocular irritation and toxicity; these findings are addressed in labeling and are similar to other products in the class.

The product is preservative free, however, no specific benefits were included as endpoints in the study, nor were any particular compliance, efficacy, or safety differences in terms of advantages noted for the PF versus the PC product. Because there is not preservative included, the instructions will state that the product is for single use and any unused portion should be discarded.

The patient package insert has been reviewed by the Office of Medical Policy and provides information on the product and its use in patient-friendly language and includes pictorial directions on how the product should be used.

13.3 Recommendation for Postmarketing Requirements (PMR) and Commitments (PMC)

None

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/s/

RENATA ALBRECHT
02/10/2012

EDWARD M COX
02/10/2012

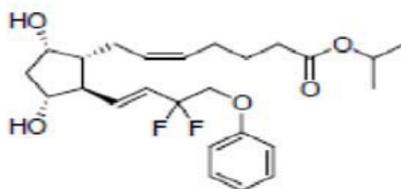
Deputy Division Director Review of NDA 202-514 (Amended Application after Complete Response Letter)

Review Date	February 1, 2012
From	Wiley A. Chambers, M.D.
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Original Submission	January 7, 2011
Date of Amendment	January 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/Background

Tafluprost (AFP-168, MK-2452) is a new chemical entity drug product proposed for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. It is an ester prodrug of a synthetic prostaglandin F_{2α} (PGF_{2α}) analog that is converted *in vivo* into the pharmacologically active tafluprost acid. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) have been approved for reducing of elevated IOP in open angle glaucoma and ocular hypertension in a number of countries including Austria, Germany, Czech Rep, Denmark, Finland, Norway, Poland, Sweden, Iceland, Italy, Spain, Portugal, the Netherlands, Romania, Bulgaria, Estonia, Latvia, Lithuania, Slovak Rep, United Kingdom, Russia, Ukraine, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan, Japan, Korea, Hong Kong, and Indonesia. Tafluprost has not been marketed in the United States.

2. CMC



The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of C₂₅H₃₄F₂O₅ and a molecular weight of 453.53 Daltons. Tafluprost is manufactured, packaged, and stability-tested at (b) (4). The information on manufacturing processes and controls for tafluprost is described in (b) (4) DMF (b) (4). All chemistry issues have been resolved.

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains tafluprost, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid to adjust to pH 5.5-6.7, and water for injection.

Glycerol is used (b) (4) of the drug product. The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. (b) (4)

The ampoules are packed (b) (4) pouches, 10 ampoules per pouch. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

COMPOSITION OF THE DRUG PRODUCT (mg per mL)

Tafluprost	0.0015
Glycerol	(b) (4)
Sodium dihydrogen phosphate dehydrate	(b) (4)
Disodium edentate	(b) (4)
Polysorbate 80	(b) (4)
NaOH/HCl	Adjust pH
Water for injection	q.s.

Regulatory Specifications:

Appearance	Clear, colorless solution. Practically free from visible particles
Tafluprost identification/HPLC, UV	Match reference standard
pH	5.5-6.7
Osmolality	260-300 mOsm/kg
Impurities	(b) (4)
Tafluprost Assay	(b) (4)
Sterility	(b) (4)
Endotoxin	(b) (4)
Particulate Matter (light obscuration/microscopy)	(b) (4)

Ophthalmic drug product specifications normally include a limit on unspecified impurities at (b) (4). The exceptions in recent years have been with products in which the concentration of the active ingredient is less than (b) (4). These exception products have had specifications for unspecified impurities listed as (b) (4) instead of a percent of the active ingredient. While it would have been preferable to list this specification (b) (4), the current proposed specification is acceptable because the concentration of the active ingredient is less than (b) (4).

(b) (4)

While it would be preferable to use the entire specification, the failure to include the full specification is not a sufficient reason by itself to not approve the product.

FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is "Acceptable" in EES.

3. Nonclinical Pharmacology/Toxicology

The active metabolite, tafluprost acid (AFP-172) is the pharmacologically active agent. In primary pharmacology studies, tafluprost acid (AFP-172) was shown to bind to the FP prostanoid receptor with subnanomolar affinity, and binding was shown to be substantially selective for this receptor.

The primary safety signals in safety pharmacology studies were a low incidence of central nervous effects in mice and a dose-dependent increase in blood pressure, heart rate, and Qtc intervals in anesthetized dogs. However, the cardiovascular effects occurred only minimally in repeated-intravenous dose toxicology studies in dogs, and did not occur in repeated-ocular dose studies in monkeys. Because clinical exposures are expected to be on the order of 100 fold lower than the exposures associated with the high ocular doses in the monkey studies, cardiovascular toxicity is not expected to be a clinical concern.

Ocular changes included iridial darkening, sunken eyelids, and blue-gray discoloration of the lower eyelid. However, all of the tafluprost-related ocular changes are consistent with ocular changes observed with other marketed PGF₂ α analogs. These effects are considered to be mainly cosmetic, not associated with loss of function, and not toxicologically significant. Other, more serious ocular toxicities including pronounced inflammation or alterations in electroretinography were not observed with topical ocular administration of tafluprost at any of the administered doses.

Topical ocular administration of 3H-tafluprost in rats and monkeys resulted in widespread ocular distribution. Repeated dosing produced a similar ocular distribution pattern, and accumulation did not occur in any tissue other than the lens where concentrations increased approximately 50% after 21 days of dosing.

Tafluprost acid was >90% bound to serum albumin from rat, rabbit, dog and humans. Tafluprost demonstrated extensive tissue distribution consistent with renal and hepatobiliary excretion and limited CNS distribution. Tissue distribution following repeated ocular dosing was similar to that following a single dose indicating an absence of systemic tissue accumulation. Tafluprost administered topically to the eye or intravenously was excreted primarily in urine and through hepatobiliary excretion with final deposition in feces.

3H-Tafluprost or its metabolites transferred into milk in lactating rats, and crossed the placental barrier in pregnant rats. Milk C_{max} radioactivity levels were similar to those in plasma, and fetal exposure was approximately two thirds that of plasma exposure.

Tafluprost was shown to be negative for genotoxicity in an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosome aberration assay in Chinese Hamster lung cells, and an *in vivo* mouse bone marrow micronucleus assay.

In both a 24-month rat carcinogenicity study and a 78-week mouse carcinogenicity study where tafluprost was administered subcutaneously, no unusual tumors or significantly increased tumor incidence suggestive of tafluprost-related carcinogenicity was observed.

4. Clinical Pharmacology/Biopharmaceutics

In four Phase 1 dose-escalation studies (74450, 74451, 74452, and 74453), neither tafluprost nor tafluprost acid could be detected when using a bioanalytical method (HPLC/MS/MS) with LLOQ at 0.2 ng/mL (tafluprost) and 0.1 ng/mL (tafluprost acid). One confounding factor is that the plasma samples may have not been stored properly in some of these studies to ensure adequate sample stability. In a subsequent Study 15005, systemic exposure following topical ocular administration of 0.0015% tafluprost ophthalmic solution was successfully assessed using an improved analytical method (HPLC/MS/MS) with LLOQ at 10 pg/mL (tafluprost acid). Furthermore, Study 77551 was conducted to verify if the systemic bioavailability of tafluprost in humans after topical ocular q.d. administration of either tafluprost (0.0015%) PF or PC ophthalmic solution is similar.

5. Sterility Assurance

This is a non-preserved aqueous solution that is sterile (b) (4) filled into single-use containers (b) (4).

(b) (4)

I disagreed with requirement to conduct three additional (b) (4) prior to approval because it does not appear to be one of the reasons to not approve an application listed in 21 CFR 314.125. The

applicant had amended their procedures to provide an acceptable procedure. The application received a complete response letter with a request for data from 3 consecutive (b) (4) processing simulations (b) (4) (b) (4) using the revised validation protocol submitted to the agency on October 27, 2011. (b) (4) batches 10019, 10020, and 10021 were manufactured separately and batch 10019 had a sterile (b) (4)

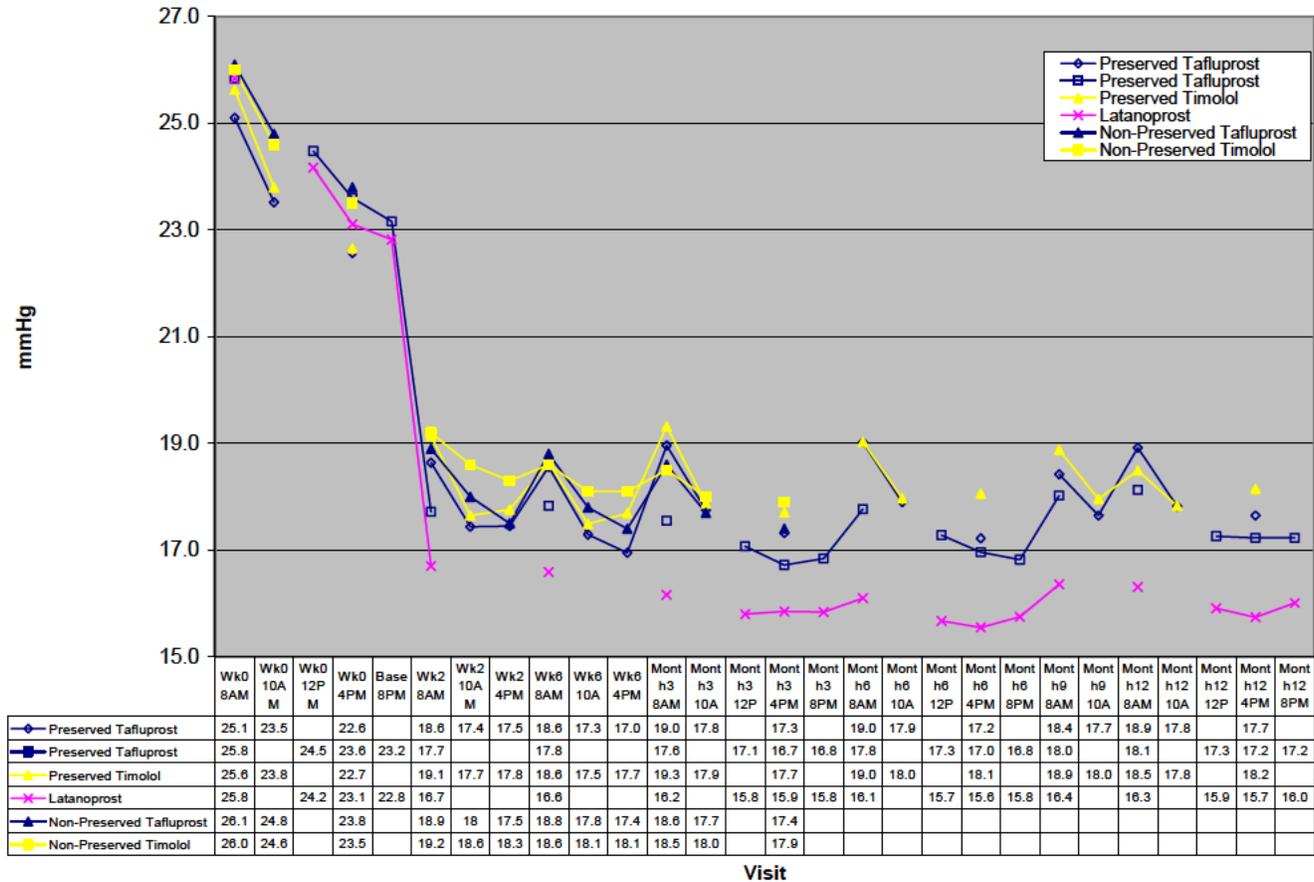
The revised (b) (4) procedures were summarized in Module 3.5.5.2 and were consistent with data reviewed for the Product Quality Microbiology Reviews #1 and #2. (b) (4) ampules were filled with (b) (4)

6. Clinical/Statistical - Efficacy

Analyses of Endpoints

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Mean IOP (Studies 001,15-003 and 74458)



As noted in the graph above, tafluprost ophthalmic solution (preserved and non-preserved) is equivalent to timolol ophthalmic solution (preserved and non-preserved) in its ability to lower intraocular pressure. The 95% confidence intervals for IOP reduction is within the equivalence margins of 1.5mmHg at all timepoints and within 1 mmHg for the majority of timepoints. Tafluprost ophthalmic solution was not demonstrated to be equivalent to latanoprost ophthalmic solution. The data support Zioptan (tafluprost ophthalmic solution) 0.0015% administered once daily in the evening for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

7. Safety

Five studies are used to support the safety and efficacy of tafluprost. The patient exposure and safety assessments were adequate.

Exposure to Study Drug by Protocol

Protocol #	Number of Patients	Tafluprost	Timolol	Latanoprost
15-002	144	87	29	28
74457	38	19		19
15-003	458	267	191	
74458	533	269		264
001	643	320	323	
Total	1816	962	543	311

Serious Adverse Events occurring in more than 1 patient (Studies 001, 15-002, 15-003, 74457, 74458)

Adverse Event	Tafluprost (n=905)	Timolol (n=543)	Latanoprost (n=311)
Retinal vein occlusion	-	2	-
Coronary artery disease	4	-	-
Chest pain	2	-	2
Death	3	-	3
Back pain	2	-	-
Syncope	-	2	-
Dyspnea	2	-	-
Hypertension aggravated	2	-	-

The most common ocular adverse events (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse event was headache (5.6%).

Adverse Events reported by $\geq 2\%$ of patients from Studies 001, 15-002, 15-003, 74457, and 74458

Adverse Event	Tafluprost (n=905)	Timolol (n=543)	Latanoprost (n=311)
Conjunctival hyperemia	97 (11%)	23 (4%)	22 (7%)
Ocular stinging/irritation	65 (7%)	38 (7%)	22 (7%)
Headache	51 (6%)	15 (3%)	15 (5%)
Ocular pruritis	44 (5%)	11 (2%)	5 (2%)
Cold	36 (4%)	13 (2%)	8 (3%)
Ocular pain	31 (3%)	15 (3%)	6 (2%)
Dry eye	27 (3%)	11 (2%)	9 (3%)
Cough	27 (3%)	9 (2%)	7 (2%)
Growth of eyelashes	21 (2%)	-	11 (3%)
Vision blurred	19 (2%)	15 (3%)	2 (1%)
Urinary tract infection	18 (2%)	6 (1%)	2 (1%)
Flu	16 (2%)	5 (1%)	12 (4%)
Eyelash darkening	15 (2%)	-	9 (3%)
Visual field constriction	12 (1%)	2 (<1%)	9 (3%)
Blepharitis	9 (1%)	3 (<1%)	7 (2%)
Cataract increased	9 (1%)	-	13 (4%)
Sinusitis	9 (1%)	3 (<1%)	8 (3%)
Hypertension	7 (1%)	0	7 (2%)
Low density lipoprotein cholesterol abnormal	4 (<1%)	0	7 (2%)

Safety Update

Merck submitted a Safety Update Report (SUR) in the response for the reporting period of March 2, 2011, to November 7, 2011. The safety data was reported to be consistent with information submitted in the original NDA. Merck reported that there were no ongoing clinical studies for tafluprost that were sponsored by Merck. There were no non-clinical studies that were either ongoing or completed during the reporting period. (b) (4)

Five of these ongoing studies are double masked. The sixth study is an open labeled long term safety study in Japan. 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) was submitted.

Post-marketing events received from market introduction April 30, 2008, to November 7, 2011, are described in an AE by system organ class table included in the submission.

The tables of reported adverse experiences/reactions were reviewed. The events were consistent with events reported in the original NDA submission. No changes in labeling are suggested based on this submission.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Zioptan (tafluprost ophthalmic solution) 0.0015%, dosed once each evening, is safe for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The most common ocular adverse events (pooled) were conjunctival hyperemia (11%) and ocular stinging/irritation (7%). The most common nonocular adverse event was headache (6%).

8. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because it is a member of the class of ophthalmic prostaglandin analogs with similar potential risks and benefits as other members in this class. The benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at a meeting of the Dermatologic and Ophthalmologic Advisory Committee on December 8, 1995, and the safety profile of tafluprost did not raise any new significant safety issues. The clinical design including endpoints of the adequate and well-controlled studies was similar to other approved drugs in this class and we are not aware of any controversial issues that would benefit from further advisory committee discussion.

9. Pediatrics

Tafluprost has not been studied in the pediatric population. The product qualifies for a waiver because of the small pediatric patient population with ocular hypertension or glaucoma. While the use in pediatric patients below the age of 16 years is not recommended because the treatment of pediatric ocular hypertension is usually a surgical treatment and there is the potential safety concern related to long term increased pigmentation following chronic use. The short term (five year use) has been studied with other prostaglandin analogs. The five year use demonstrated that increased pigmentation continues throughout the period, but at five years there were no adverse consequences.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. Per the DSI review finalized 6/27/2011:

Two clinical sites were inspected in support of this application. In general, inspection of Dr. Douglas Day's site revealed that he adhered to the applicable regulations and good clinical practices governing

the conduct of clinical investigations and the final classification for this inspection is No Action Indicated (NAI).

Inspection of Dr. David Wirta's site documented regulatory violations and the preliminary classification for this inspection is Voluntary Action Indicated (VAI) for errors in recordkeeping of adverse events, which were isolated and relatively minor. Incorrect causality of adverse events was corrected and later reported to the sponsor.

The studies at these sites appear to have been conducted adequately, and the data generated may be used in support of the application.

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment considered originally proposed proprietary name, Saflutan. In an April 15, 2011, letter to the applicant DMEPA found this proprietary name unacceptable since it is orthographically similar to, and shares overlapping product characteristics with, Xalatan.

In an August 31, 2011, letter to the applicant, DMEPA found the proprietary name Zioptan to be acceptable.

DMEPA was invited to all internal labeling meeting and provided recommendations on the packaging configuration and the package insert labeling.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)/DIVISION OF PROFESSIONAL PROMOTION (DPP)

OPDP provided labeling comments based on the substantially complete version of the labeling titled, "N202514_Label1.doc" which was sent via email from Constantine Markos on October 17, 2011.

The warning against use of contact lenses with the use of other prostaglandin analogs is not applicable to tafluprost since it does not contain a preservative which can be absorbed into the contact lenses and remain in contact with the eye.

BIOSTATISTICS

Per the Biostatistics consultative review:

The Applicant submitted three non-inferiority efficacy studies (two timolol non-inferiority studies [15-003 and 001] and one Latanoprost Non-Inferiority Study [74458]), and a study comparing the PC formulation and PF formulation (Study 77550).

For study 15-003 comparing preservative-containing (PC) tafluprost with PC timolol, both PC tafluprost and the active comparator PC timolol showed IOP-lowering effect throughout the 12-month study period. Tafluprost reached the predetermined criteria for non-inferiority (1.5 mmHg) at each visit and time point using timolol as the active comparator.

For study 001 comparing PF tafluprost versus PF timolol, both PF tafluprost and the active comparator (PF timolol) showed IOP-lowering effect throughout the 12 weeks of treatment. The IOP-lowering effect of PF tafluprost was within the 1.5 mmHg non-inferiority margin compared to PF timolol at all visits and time points.

Study 77550 investigated the pharmacodynamics (as expressed in IOP) of the preserved and unpreserved formulation of tafluprost 0.0015% eye drops in patients with open-angle glaucoma or ocular hypertension. For both the preservative-containing and preserve-free formulation, a similar and clear IOP-lowering effect was seen already at week 1 and the IOP-lowering effect was sustained and similar for both formulations at week 4.

For study 74458, both PC tafluprost and PC latanoprost reduced IOP throughout the 24 months treatment period. However, tafluprost did not reach the predetermined criterion for noninferiority (1.5 mmHg) versus latanoprost. Using the non-inferiority margin of 1.5 mmHg, both studies 15-003 and 001 demonstrated noninferiority of tafluprost 0.0015% to timolol 0.5% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in both preservative-containing and preservative-free formulation. Study 77550 demonstrated that the IOP lowering effects for the PC formulation and the PF formulation were similar.

Based on the totality of the evidence provided by these pivotal studies, we recommend the approval of PF tafluprost 0.0015% dosed once daily for the treatment of elevated intraocular pressure in patients with open glaucoma or ocular hypertension.

11. Labeling

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the labeling below.

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

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

/s/

WILEY A CHAMBERS
02/01/2012