CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208582Orig1s000

STATISTICAL REVIEW(S)

Statistics Filing Checklist for NDA - 208582

NDA Number:	208582
NDA Type:	Priority Review
Drug Name:	(b) (4) Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution USP (0.25%/0.4%))
Indication:	For ophthalmic procedures requiring a disclosing agent in combination with anesthetic agent (b) (4) (b) (4)
Applicant:	Altaire Pharmaceuticals, Inc.
Stamp Date:	December 22, 2015
Reviewer:	Yunfan Deng

1. Brief Summary of Controlled Clinical Trial(s)

The submission is a 505(b)(2) new drug application that solely relies on published literature and the long history of ophthalmic use of this combination product and its each individual ingredients. There were no pivotal studies conducted by the applicant for this product.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			☑	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			☑	
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			☑	
Appropriate references for novel statistical methodology (if present) are included.			☑	
Safety data organized to permit analyses across clinical trials in the NDA.			☑	
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.			☑	

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	N/A
Dataset structure (e.g., SDTM or ADaM)	N/A
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	N/A
List the dataset(s) that contains the primary endpoint(s)	N/A
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	N/A
Are the define files sufficiently detailed?	N/A
Safety data are organized to permit analyses across clinical trials in the NDA.	N/A

4. Filing Issues

Table 4: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.			☑	
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			☑	
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			☑	
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).			☑	

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?

During the filing meeting, the statistical reviewer commented that the published studies submitted in this NDA appeared to use the combination product or its individual components as an active control to evaluate the effectiveness of other products. The statistical team raised the question on how these studies could be used to evaluate the efficacy of the combination product. The clinical review team responded that in clinical practice the combination product is used as a gold standard for the proposed indication and its efficacy was demonstrated not through the typical clinical trials. Therefore the statistical team defers the filability decision to the clinical review team and agrees with the clinical team that the statistical team doesn't need to write a separate statistical review for this NDA.

Appendix 1: Brief Summary of NDA208582

Submission Background

The applicant seeks approval of (b) (4) (Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution USP (0.25%/0.4%)) through this submission of a 505(b)(2) new drug application that relies on published literature and the long history of ophthalmic use of this combination product and the individual ingredients. The proposed indication for this product is "for ophthalmic procedures requiring a disclosing agent in combination with an anesthetic agent (b) (4)
(b) (4)

According to the applicant, evidence from five studies suggests that Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution provides fluorescence and anesthesia sufficient to facilitate the assessment of IOP by Goldmann applanation tonometry (GAT) and that this combination product is at least as effective as other combinations that contain a different anesthetic and/or fluorophore. Furthermore, compared to GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution, GAT using only an anesthetic significantly underestimated IOP, particularly among patients with elevated IOP. The following is a brief summary of these five studies.

Bright et al.

In this crossover trial, patients (n=100) underwent bilateral assessment of IOP by GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution and using Proparacaine 0.5% Ophthalmic Solution. To minimize order effects, the first eye assessed (OD [right eye] or OS [left eye]) and the first treatment used were selected randomly, and one eye from each patient was randomly selected as the study eye. A matched-pairs analysis was used to compare IOP assessed using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution to that assessed using Proparacaine 0.5% Ophthalmic Solution. GAT conducted without Fluorescein gave significantly lower IOP readings than GAT conducted with Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution when the same eyes were assessed (difference: 7.01 mm Hg, $p<0.001$). The correlation between IOP readings assessed with and without Fluorescein was significant ($r=0.552$, $p<0.01$). A linear regression analysis found that GAT without Fluorescein tended to underestimate IOP to a greater extent in eyes with higher IOP. While all patients received Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution in both eyes; tolerability and AEs were not reported.

Jose et al.

In this crossover trial, patients (n=14) underwent bilateral assessment of IOP by GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution and using Proparacaine 0.5% Ophthalmic Solution and a Fluorescein strip. For each subject, the order of drug instillation was determined randomly, by a coin flip. Between drugs, eyes were irrigated to flush out any remaining solution and after a 20-minute waiting period the next drug combination was instilled. For each drug combination, three successive measurements were taken and averaged. IOP assessed by GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution was lower than that assessed by GAT using 0.5% Proparacaine Ophthalmic Solution and Fluorescein strip (difference: 0.82 mm Hg, $p<0.05$); however, the difference was relatively small and did not appear to be clinically

meaningful. While all patients underwent GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution in both eyes, no safety and/or tolerability findings were reported.

Quickert et al.

In this double-masked crossover trial, patients (n=50) underwent bilateral assessment of IOP by GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution and using Proparacaine 0.5% and 0.25% Fluorescein Ophthalmic Solution. The treatment order was varied to minimize order effects. Anesthesia and fluorescence were adequate for both solutions. After administration of Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution, 30 patients reported no stinging, 17 reported mild/moderate stinging, and three reported marked stinging. After administration of Proparacaine 0.5% and 0.25% Fluorescein Ophthalmic Solution, 37 patients reported no stinging, 13 reported mild/moderate stinging, and two reported marked stinging.

Ng et al.

In this randomized, double-masked crossover trial, patients (n=67) underwent bilateral assessment of IOP by GAT using Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution and Benoxinate 0.4% and 0.35% Fluorexon Disodium Ophthalmic Solution. Patients were randomly assigned to receive one of the drugs in both eyes on Day 1 and received the other drug on Day 8. Mean IOPs did not differ significantly between the Fluorescein group and the Fluorexon-disodium group (OD, difference: 0.0 mm Hg, p=NS; OS, difference: 0.1 mm Hg, p=NS). Bland-Altman analysis indicated that the differences between solutions was independent of the level of IOP. The Pearson correlation coefficient between IOP measurements of the same eye using each solution was 0.79 (95% confidence interval [CI]: 0.68, 0.87) for OD and 0.763 (95% CI: 0.64, 0.85) for OS. An investigator survey found no significant differences between treatments in visibility of the mires and adequacy of fluorescence and anesthesia. Investigators reported post-GAT corneal damage in some patients after receiving the Fluorescein formulation (n=11) and in some after receiving the Fluorexon disodium formulation (n=4); the difference was not statistically significant (p=0.071). After receiving each formulation, some patients reported discomfort (Fluorescein: n=20; Fluorexon disodium: n=13), soreness or irritation (Fluorescein: n=10; Fluorexon disodium: n=8), and burning or stinging (Fluorescein: n=17; Fluorexon disodium: n=11). At one-minute post-instillation, discomfort (p=0.039) and burning/stringing (p=0.014) were significantly greater in the Fluorescein group; however, no significant differences were seen at five minutes post-instillation.

Hales

In this study, Hales reported that Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution was used for the assessment of IOP by GAT in 1,381 patients aged 5–96 years. The age range indicates that the product was used in some pediatric patients (n=not reported). In 1,379 of 1,381 patients, one drop of Benoxinate 0.4% and 0.25% Fluorescein Ophthalmic Solution provided adequate anesthesia for a GAT procedure. In two eyes (from two patients), a second drop of the solution was required to achieve adequate anesthesia—both eyes had preexisting inflammation (secondary to recent thermal sclerotomy and angle-closure glaucoma). In both cases, a single drop was sufficient in unaffected fellow eyes. Some patients (n=NR) experienced a burning sensation in their eyes after instillation. Discomfort was described as similar to that seen with Proparacaine HCl and less than that seen with Tetracaine HCl. No allergic reactions, toxic reactions, or infections were reported.

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/s/

YUNFAN DENG
03/09/2016

YAN WANG
03/09/2016