CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 9, 2012
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 202-236/ SN000
Applicant	Meda Pharmaceuticals, Inc.
Date of Submission	April 1, 2011
PDUFA Goal Date	May 1, 2012
Proprietary Name / Established (USAN) names	Dymista Nasal Spray (azelastine hydrochloride/ fluticasone propionate)
Dosage forms / Strength	Azelastine hydrochloride 137 mcg/fluticasone propionate 50 mcg per spray (0.1%/0.037%)
Proposed Indication(s)	1. Seasonal allergic rhinitis in patients 12 years and older
Recommended:	Approval

1. Introduction

Meda Pharmaceuticals, Inc. submitted a 505(b)(2) new drug application (NDA #202-236) on April 1, 2011, for a fixed-dose combination nasal spray containing azelastine hydrochloride 0.1% and fluticasone propionate 0.037% for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Each actuation of the nasal spray pump delivers 137 mcg azelastine and 50 mcg fluticasone propionate. The proposed dosing regimen is 1 spray to each nostril twice daily, so that the total daily dose is 548 mcg azelastine hydrochloride and 200 mcg fluticasone propionate. The proposed tradename is Dymista. The drug product represents the first fixed-dose combination nasal spray for an allergic rhinitis indication. The individual components, azelastine hydrochloride and fluticasone propionate, are each approved for various rhinitis indications and are currently marketed in several different formulations.

The application was initially submitted on April 1, 2011, and was filed as a standard review. The Applicant submitted an amendment on December 7, 2011, containing CMC information on the pharmaceutical characteristics of the novel monocomparators used in the key efficacy trials. As this information was critical for the interpretation of the clinical trial results, the amendment was considered to be a major amendment, and the review clock was extended by three months.

Throughout this memo, the drug product for this application will be referred to as azelastine hydrochloride/fluticasone propionate (azelastine/FP). This memo will provide an overview of the application with a focus on the data that support the contribution of each monocomponent to the efficacy and safety of the fixed-dose combination. As part of this discussion, the memo

will discuss the regulatory background for the program, given its status as the first fixed-dose combination nasal spray.

2. Background

Azelastine hydrochloride
Azelastine hydrochloride is a selective, H_1 antihistamine, and is approved in the US in an ophthalmic solution, Optivar, and in two nasal spray solutions, Astelin Nasal Spray and Astepro Nasal Spray. Astelin Nasal Spray (azelastine hydrochloride 0.1%) was originally approved in the US in November 1996 for the treatment of SAR and is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide and has nonprescription status in many of these countries. According to the Applicant, there have been no marketing withdrawals, suspensions, failure to obtain renewal, restrictions on distribution, or clinical trial suspensions worldwide.

Astelin Nasal Spray is currently approved for the following indications in the US:

- Seasonal allergic rhinitis (SAR)
  - Children 5 to 11 years - 1 spray per nostril BID
  - Adults and children 12 years of age and older -1 or 2 sprays per nostril BID
- Vasomotor rhinitis (VMR) in adults and children 12 years of age and older - 2 sprays per nostril twice daily

Azelastine hydrochloride is characterized by a bitter aftertaste. To mask the taste, Meda also developed a formulation of azelastine hydrochloride nasal spray which contained two additional excipients, sucralose and sorbitol. The sweetened formulation is marketed under the tradename Astepro Nasal Spray 0.1% and 0.15% (NDA 22-203 and 22-371). Astepro 0.1% was approved in 2008 for SAR in patients 12 years and older in 2008, and Astepro 0.15% was approved for SAR and perennial allergic rhinitis (PAR) in patients 12 years and older in 2010.

Fluticasone propionate
Fluticasone propionate is a corticosteroid available as an intranasal formulation (Flonase, NDA 20-121, approval date 1994, GSK) and as an orally inhaled formulation (Flovent Diskus, NDA 20-833; Flovent HFA, NDA 21-433).

Flonase Nasal Spray is currently approved for SAR, PAR, and nonallergic rhinitis (NAR) in patients 4 years and older at the following doses:

- Adults and children 12 years and older:
  - 2 sprays per nostril QD (200 mcg/day)
  - 1 spray per nostril BID (200 mcg/day)
  - In some patients, the dose may be decreased to 1 spray per nostril QD (100 mcg/day)
- Children 4 to 11 years
  - 1 spray per nostril once daily (100 mcg/day)
  - Some pediatric patients may require 200 mcg/day, delivered as 1 spray per nostril BID or 2 sprays per nostril QD

A combination nasal spray containing azelastine hydrochloride and fluticasone propionate (Duonase) at the same nominal doses is currently marketed in India, but the formulation differs from the proposed azelastine/FP product which is the subject of this application.

Regulatory background
As noted in the Introduction, azelastine/FP will be the first fixed-dose combination nasal spray approved for allergic rhinitis. The development of an intranasal antihistamine/corticosteroid combination raised certain issues that had not been previously encountered in development programs for single-component nasal sprays. Early in development, the Division highlighted the need to satisfy the requirements of the Combination Rule outlined in 21CFR 300.50. Specifically, the Division expressed concerns regarding the following: 1) identification of an appropriate patient population for the proposed product; 2) the loss of dose titration flexibility; 3) the use of two components to treat the same symptoms of allergic rhinitis; and 4) the need for pharmaceutically comparable monocomparators to be used in the key factorial-design trials (May 21, 2007 written communication; September 10, 2007 Type A Meeting Minutes; January 31, 2008 SPA No Agreement Letter).

Given the multiple issues surrounding the interpretation of the Combination Rule in the azelastine/FP program, the Agency held a Regulatory Briefing on April 17, 2009. Based on the feedback received in this internal discussion, the Division communicated to the Applicant in an April 23, 2009, teleconference, that the Agency would accept a fixed-dose combination product where each monotherapy component treats the same symptoms of allergic rhinitis. Furthermore, the demonstration of a statistically significant difference between azelastine/FP and each of the monocomparators would be accepted as evidence of a patient population requiring concurrent therapy, provided that the effect sizes were of reasonable magnitude and each monocomparator also demonstrated superiority to placebo. The Division noted that statistical significance driven by a large sample size with a marginal treatment effect would likely be inadequate.

In addition, the Division reiterated the requirement for demonstrating that there were no pharmaceutical differences between the combination product and each monocomponent. Due to the pharmaceutical differences between the corresponding commercial monoproducts and the azelastine/FP combination formulation, the Applicant was compelled to develop monocomparators specifically for the azelastine/FP program. As the monocomparators developed specifically for the azelastine/FP program were novel products, replicate evidence of efficacy for each monocomparator versus placebo was also expected.

3. CMC/Device

The application is recommended for Approval from a CMC perspective, provided that the Office of Compliance issues an acceptable recommendation for all manufacturing and testing sites.

- General product quality considerations

The drug product, azelastine hydrochloride/fluticasone propionate (A/FP), is a fixed-dose combination of an intranasal antihistamine and corticosteroid, respectively. The drug product is a suspension nasal spray, supplied in a multi-dose, amber glass bottle and fitted with a metered (b) (4) spray pump. Each spray delivers 137 mcg azelastine (equivalent to 125 mcg azelastine base) and 50 mcg fluticasone propionate. The drug contains an isotonic, (b) (4) aqueous formulation of 0.1% azelastine hydrochloride and suspended, micronized 0.037% fluticasone propionate USP with a pH 6.0 (b) (4) The excipients consist of glycerin, microcrystalline cellulose and carboxymethylcellulose sodium (b) (4) polysorbate 80, edetate disodium (EDTA), benzalkonium chloride (0.1 mg/g), phenylethyl alcohol (2.5 mg/g), and purified water.

The fill weight of 23 g delivers at the minimum 120 sprays after priming (commercial pack), and the fill weight of 6 g delivers at the minimum 28 sprays after priming (sample pack). The submitted CMC data support a 24-month expiry period when the product is stored at 20°-25°C (68°-77°F).

Initial review of the CMC data noted deficiencies in the proposed specifications, analytical methods, and stability data for the drug product as described in the June 13, 2011, 74-day filing letter. In addition, the review team expressed concerns regarding the ruggedness of the container closure device, noting that the actuator detached easily from the glass vial during removal of the dust cap. Subsequently, the Applicant proposed new acceptance criteria for spray weight, spray content uniformity, droplet size distribution, and the microscopic method for particle size distribution. The original proposed expiry period (b) (4) was not adequately supported given out-of-trend instability changes for several tested attributes, so the expiry period was modified to 24 months. Manufacturing changes were also implemented to seat the actuator more securely on the glass vial. As the changes are not anticipated to substantially impact dose performance, the proposed changes were considered acceptable, and comparative data comparing the dose performance of the drug product before and after the changes will be submitted in the first annual report. The CMC review team has concluded that the deficiencies have been addressed by the Applicant's responses, and that the proposal for follow-up information is acceptable.

- Facilities review/inspection

The Establishment Evaluation Request (EER) for this NDA is pending at the time of this memorandum. Azelastine hydrochloride is manufactured by (b) (4) and fluticasone propionate is manufactured by (b) (4) The drug product is manufactured by Cipla Ltd. in Goa, India. Acceptable status is indicated in the EES for the (b) (4) Voluntary Action Indicated (VAI) status is listed in the EES for the azelastine hydrochloride drug substance manufacturing site (b) (4) The cGMP inspection was completed at this establishment in July 2011, with a FDA Form 483 issued.

- Other notable issues (resolved or outstanding)

Given the requirements outlined by the Combination Rule in 21CFR 300.50, characterization of the monocomponents in the fixed-dose combination for potential pharmaceutical interactions as well as characterization of the monocomparators used in the key efficacy and safety trials was a focus of the CMC review for this application. While azelastine and fluticasone propionate are marketed as individual products, the formulation of the commercially available products differs from the formulation of the combination. In the combination, azelastine is solubilized in the drug product formulation while the fluticasone propionate is micronized and in suspension. Therefore, the Applicant developed novel azelastine 0.1% nasal spray and fluticasone propionate 0.037% nasal spray monocomparator products specifically for use in the key factorial design clinical trials.

Dose performance comparison data for the combination and monotherapy products were reviewed and found to be comparable. (b) (4) the overall dose performance results were considered to be within the acceptable range of variations of NMT (b) (4) Based on the in vitro data, the CMC review team has concluded that there are no significant pharmaceutical interactions, which would potentially impact the interpretation of the clinical results.

4. Nonclinical Pharmacology/Toxicology

The recommendation from the Nonclinical Pharmacology/Toxicology review is Approval. There are no outstanding issues from a pharmacology/toxicology perspective at this time.

The nonclinical program for azelastine/FP is based upon complete toxicology programs conducted for the individual active drugs, including single dose toxicology, subchronic toxicology, chronic toxicology, reproductive toxicology, genotoxicity, and carcinogenicity studies. These studies were previously reviewed under NDAs 20-114 and 20-121. The Applicant conducted 14-day intranasal toxicology studies in rats and dogs and a 3-month intranasal toxicology study in rats with azelastine/FP. In general, these toxicology studies did not indicate any potential additive or synergistic toxic effects of the combination. Mast cells were noted to be increased in the mandibular lymph nodes of both male and female rats in the azelastine/FP group compared to control, vehicle, and the monoproducts, but the toxicological significance of this finding is uncertain given that high background levels in the tracheobronchial lymph nodes of control males were also observed. Azelastine/FP is categorized as Pregnancy Category C.

5. Clinical Pharmacology/Biopharmaceutics

The application is deemed acceptable from a Clinical Pharmacology perspective. No issues are outstanding at this time.

The clinical pharmacology program for this application included two single-dose relative bioavailability trials in healthy volunteers to assess for potential drug-drug interactions and formulation issues (X-03065-3282 and X-03065-3283). These trials demonstrated that co-

administration of azelastine and fluticasone does not affect the systemic exposure of either. Systemic exposure for azelastine in combination is within ±20% exposure of the commercially marketed azelastine product, Astelin. In contrast, systemic exposure for FP in combination is 44 to 61% higher than exposure from a commercially marketed, generic FP nasal spray product at the same nominal dose. However, the systemic exposure of FP from the azelastine/FP combination is below the systemic exposure from higher doses of commercially marketed FP nasal spray (Flonase 200 mcg once daily or 400 mcg twice daily), which has been reported to have no effect on adrenal responses and is described in the current Flonase package insert. While a HPA-axis study has not been conducted specifically for azelastine/FP, the information regarding relative systemic exposures suggests that the higher systemic exposure observed for FP in azelastine/FP is not likely to pose new systemic safety concerns. Previously, at the Pre-NDA meeting held on August 17, 2010, the Division had agreed that if systemic exposure from azelastine/FP were equal or less than systemic exposures from the corresponding commercially marketed monotherapies, then a separate HPA axis trial would not be required.

Information on drug interactions, intrinsic factors, demographic interactions, and QT assessment are based on clinical pharmacology data for the commercially marketed monocomponent drugs that are described in the respective package inserts. No dose adjustments are recommended for renal or hepatic impairment or for geriatric patients. The application references previous trials that evaluated potential cardiac effects of both intranasal and oral azelastine; no QT effect was observed with intranasal azelastine, while mean changes in QTc of 7.2 msec and 3.6m msec have been observed following multiple-dose, oral administration of azelastine 4 mg and 8 mg twice daily, respectively. The clinical program for azelastine/FP did not include a thorough QT assessment.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical- Efficacy

The main clinical program for azelastine/FP consisted of five efficacy and safety trials: 4001, 4002, 4004, 4006, and 4000 (Table 1). Trial 4000 was a long-term safety trial and is discussed separately in the following Section 8 on safety. The clinical program also included two clinical pharmacology trials (X-03065-3282 and X-03065-3283), which were discussed previously in Section 5 Clinical Pharmacology/Biopharmaceutics. This section focuses on the trials which demonstrated the contribution of azelastine and FP to the efficacy of the combination product and which form the basis for the recommended regulatory decision, namely, trials 4002, 4004, and 4006.

The results of 4001 are of clinical interest, however, 4001 is viewed as secondary support due to the use of Astelin and commercially marketed FP as monocomparators. Given pharmaceutical differences between the commercial formulations and the azelastine/FP formulation, the commercial monoproducts are not appropriate comparators for the purpose of

addressing the Combination Rule. For this reason, the results of 4001 will be summarized briefly but will not be a focus of this section.

Table 1 Azelastine/FP efficacy and safety trials

Trial *Trial dates*	Design	N[1]	Treatment[2]	Endpoints	Sites
4001 *Dec 2007 to Feb 2008*	2-week, R, DB, PC, AC trial in patients 12 years and older with SAR (Texas Mountain Cedar)	153 153 153 151	Azelastine/FP Astelin Commercial FP Placebo	Change from baseline in rTNSS	US
4002 *Mar 2008 to Jun 2008*	2-week, R, DB, PC, AC, trial in patients 12 years and older with SAR	207 208 207 210	Azelastine/FP Azelastine FP Placebo	Change from baseline in rTNSS	US
4004 *Aug 2008 to Nov 2008*	2-week, R, DB, PC, AC trial in patients 12 years and older with SAR	195 194 189 201	Azelastine/FP Azelastine FP Placebo	Change from baseline in rTNSS	US
4006 *Apr 2009 to Aug 2009*	2-week, R, DB, PC, AC trial in patients 12 years and older with SAR	451 449 450 451	Azelastine/FP Azelastine FP Placebo	Change from baseline in rTNSS	US
4000 *Jan 2008 to Jun 2009*	12-month, R, OL, AC trial in patients 12 to 80 years of age with PAR or VMR	405 207	Azelastine/FP Commercial FP[2]	Safety	India

[1] number randomized

[2] All treatments administered as 1 spray per nostril BID except in Trial 4000, where the commercial FP active control was administered as 2 sprays per nostril BID.

Dose selection

The proposed dose of 1 spray to each nostril twice daily delivers a total daily dose of 548 mcg azelastine and 200 mcg fluticasone propionate. Azelastine/FP is viewed as a combination of convenience, and formal dose-ranging trials of the combination were not conducted. Dose selection for each component of azelastine/FP is based on the approved dosing for each individual component and supported by the efficacy and safety data obtained in the Phase 3 program.

As mentioned in the preceding Background section, the Division had initial concerns that patients may be exposed to doses higher than necessary to treat their symptoms, since the fixed-dose formulation would eliminate the option for dose titration that is recommended for FP. This issue is discussed in further detail in Section 12 on Labeling.

Trial design

Trials 4001, 4002, 4004, and 4006 were 2-week, randomized, double-blind, placebo- and active-controlled trials in patients 12 years and older with seasonal allergic rhinitis. The trials had a full factorial design, intended to demonstrate the contribution of each monocomponent to the combination to satisfy the requirements of the Combination Rule. After a 7-day, single-blind, placebo lead-in period, patients 12 years of age and older with a minimum 2-year history of SAR to a relevant local allergen and a positive skin test were randomized 1:1:1:1 to azelastine/FP, azelastine, FP, or vehicle placebo administered 1 spray per nostril twice daily. Patients were required to have a minimum symptom score and a demonstration of compliance

with the placebo spray during the run-in period in order to be randomized. Information regarding patients' history of prior experience with azelastine or FP nasal sprays was not specifically queried.

During the 14-day treatment period, patients recorded reflective and instantaneous total nasal symptom scores (TNSS) twice daily. The TNSS was defined as the sum of the nasal symptom scores of itchy nose, nasal congestion, runny nose, and sneezing, rated on a 4-point scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2= moderate symptoms, and 3 = severe symptoms). In addition to the rTNSS and iTNSS, patients scored reflective and instantaneous total ocular symptom scores (TOSS), defined as the sum of the ocular symptoms of itchy eyes, watery eyes, and eye redness on a 4-point scale (0 = no symptoms, 1 = mild symptoms, 2= moderate symptoms, and 3 = severe symptoms). Patients who were 18 years or older also completed a Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ), a 28-item questionnaire that scores the subjective impact of SAR symptoms on quality of life. A change from baseline of ≥0.5 units is considered to be a minimum clinically important difference (MCID) for the RQLQ, and a treatment difference of ≥0.5 units between comparator arms is also expected.

In general, the patient population, trial design, and assessments were consistent with the recommendations outlined in the *Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products* (April 2000) and the clinical trials conducted for other allergic rhinitis programs. The primary endpoint was the change from baseline over the 14-day treatment period in the combined AM and PM rTNSS. Instantaneous TNSS was also assessed to confirm the dosing interval as well as to establish the onset of action. In Trials 4004 and 4006, the change from baseline over the 14-day treatment period in the combined AM and PM rTOSS was designated as a key secondary endpoint. The change from baseline in the RQLQ was assessed as an additional secondary endpoint in all the trials.

The trials were similar in conduct and size, with the exception of Trials 4001 and 4006. As noted, Trial 4001 used corresponding commercial products for the monocomparator arms. Trial 4006 enrolled 1801 patients, which was more than double the size of the other Phase 3 trials. The Applicant stated in the August 17, 2010, pre-NDA meeting that the trial was powered based on the magnitude of effect observed in the preceding Trial 4002 (b) (4) (b) (4) This (b) (4) is discussed in further detail below.

Efficacy results

Reflective TNSS

The key trials, Trials 4002, 4004, and 4006, demonstrated a statistically significant decrease in the combined AM and PM rTNSS scores over the 14-day treatment period for the comparison of azelastine/FP to placebo (Table 2). Comparisons of the azelastine and FP monocomparators to placebo were also statistically significant ($p<0.001$; results not shown in table). The factorial comparisons of azelastine/FP to the individual monocomparators, azelastine and FP, were also statistically significant, with the exception of the borderline results in Trial 4004 for the comparison of azelastine/FP to FP alone ($p=0.06$; Table 2). These results provide replicate

evidence of the contribution of each individual component to the efficacy of the combination, satisfying the requirements of the Combination Rule and demonstrating the advantage of the combination over each individual component. The magnitude of the treatment differences was similar to the differences observed in other clinical programs for allergic rhinitis, and the results based on last-observation-carried-forward (LOCF) imputed and non-imputed results were also similar. The pre-specified analysis was based on a repeated-measures analysis using the last observation carried forward (LOCF) method for imputation of missing data. As there are some concerns regarding the use of LOCF imputation in this setting, the results presented here are based on observed data without imputation (Table 2). The issue of imputation and different sensitivity analyses are discussed in further detail in the biostatistical review.

Table 2 Results of change from baseline in rTNSS over 2 weeks (observed data)

Treatment	N	Baseline LS Mean	Change from baseline LS Mean	Treatment Difference from Azelastine/FP		
				LS Mean	95% CI	P-value
4002						
Azelastine/FP	207	18.27	-5.64	--	--	--
Azelastine	208	18.26	-4.28	-1.37	(-2.22, -0.52)	0.002
FP	207	18.22	-4.67	-0.97	(-1.80, -0.24)	0.022
Placebo	209	18.61	-2.94	-2.71	(-3.49, -1.92)	<0.001
4004						
Azelastine/FP	193	18.28	-5.54	--	--	--
Azelastine	193	18.54	-4.53	-1.01	(-1.92, -0.10)	0.030
FP	188	18.64	-4.66	-0.88	(-1.79, 0.04)	0.060
Placebo	199	18.24	-3.12	-2.41	(-3.24, -1.58)	<0.001
4006						
Azelastine/FP	448	19.34	-5.55	--	--	--
Azelastine	443	19.47	-4.80	-0.75	(-1.33, -0.16)	0.012
FP	450	19.41	-4.91	-0.64	(-1.21, -0.06)	0.030
Placebo	448	19.44	-3.39	-2.16	(-2.72, -1.59)	<0.001

Results for the comparison of azelastine/FP to placebo for each of the individual rhinitis symptoms (itchy nose, nasal congestion, runny nose, and sneezing) were also statistically significant ($p<0.001$).

Results for Trial 4001, the trial that used commercial azelastine and FP, were similar to the results observed for the other efficacy trials. Statistically significant differences for the comparison of azelastine/FP to placebo, Astelin, and generic commercial FP were observed.

Instantaneous TNSS

The key trials demonstrated a statistically significant decrease in instantaneous TNSS for azelastine/FP compared to placebo and for each of the monocomparators compared to placebo, supporting the proposed dosing interval of twice daily (Table 3).

Table 3 Results of change from baseline in iTNSS over 2 weeks (observed data)						
Treatment	**N**	**Baseline LS Mean**	**Change from baseline LS Mean**	**Treatment Difference from Placebo**		
				LS Mean	**95% CI**	**P-value**
4002						
Azelastine/FP	207	17.16	-5.21	-2.55	(-3.35, -1.76)	<0.001
Azelastine	208	16.84	-3.91	-1.25	(-1.96, -0.55)	<0.001
FP	207	16.84	-4.54	-1.89	(-2.60, -1.18)	<0.001
Placebo	209	17.26	-2.66	--	--	--
4004						
Azelastine/FP	193	17.16	-5.19	-2.63	(-3.43, -1.82)	<0.001
Azelastine	193	17.28	-4.14	-1.57	(-2.36, -0.78)	<0.001
FP	188	17.19	-4.40	-1.83	(-2.64, -1.02)	<0.001
Placebo	199	16.84	-2.57	--	--	--
4006						
Azelastine/FP	448	17.91	-5.01	-1.92	(-2.49, -1.35)	<0.001
Azelastine	443	18.00	-4.31	-1.22	(-1.76, -0.68)	<0.001
FP	450	17.82	-4.73	-1.64	(-2.19, -1.09)	<0.001
Placebo	448	17.90	-3.09	--	--	--

The iTNSS scores were also used to characterize the onset of action, defined as the first time point after initiation of treatment when azelastine/FP demonstrated a statistically significant difference from placebo in terms of the reduction in iTNSS which proved durable from that timepoint. An onset of action of 30 minutes was demonstrated in replicate in 4004 and 4006; the onset of action in 4002 was 45 minutes.

Reflective TOSS

The change in mean rTOSS from baseline over the 14-day treatment period was assessed as secondary efficacy endpoint, (b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

RQLQ

The change from baseline in RQLQ over the 14-day treatment period was an additional secondary endpoint, and the Applicant proposes inclusion of RQLQ information in the product label. The comparison of azelastine/FP to placebo was statistically significant in all three trials and crossed the MCID threshold of ≥0.05 units; these replicate results are considered adequate to support inclusion of RQLQ information in the product label.

Table 5 Results of change from baseline in RQLQ over 2 weeks (ITT population, excluding patients with missing baseline value)

Treatment	N	Baseline LS Mean	Change from baseline LS Mean	Treatment Difference from Azelastine/FP		
				LS Mean	95% CI	P-value
4002						
Azelastine/FP	176	3.87	-1.64	--	--	--
Azelastine	174	3.80	-1.36	-0.29	(-0.54, -0.03)	0.029
FP	184	3.76	-1.63	-0.01	(-0.36, 0.23)	0.907
Placebo	169	3.87	-0.85	-0.80	(-1.05, -0.55)	<0.001
4004						
Azelastine/FP	176	3.76	-1.68	--	--	--
Azelastine	172	3.83	-1.40	-0.28	(-0.53, -0.03)	0.031
FP	169	3.78	-1.48	-0.20	(-0.46, 0.05)	0.123
Placebo	171	3.88	-0.97	-0.71	(-0.97, -0.45)	<0.001
4006						
Azelastine/FP	381	3.87	-1.59	--	--	--
Azelastine	394	3.92	-1.42	-0.17	(-0.33, -0.01)	0.043
FP	384	3.87	-1.55	-0.04	(-0.20, 0.12)	0.629
Placebo	393	3.88	-1.03	-0.55	(-0.72, -0.39)	<0.001

Summary of efficacy

The application contains adequate data to support the efficacy of azelastine/FP for the treatment of symptoms of seasonal allergic rhinitis in patients 12 years and older. The three key trials (4002, 4004, and 4006) demonstrated statistically significant results for the pre-

specific efficacy endpoint, the change from baseline in mean rTNSS over the 14-day treatment period. While there is no agreed-upon MCID for the rTNSS, the magnitude of the treatment effect observed was fairly consistent across the three trials as well as in comparisons with other allergic rhinitis clinical programs. Two of the three trials (4004 and 4006) also provided robust, statistically significant demonstration of factorial contribution of azelastine and FP to the combination. These results address the requirements for a combination product as outlined in the Combination Rule and provide justification for the use of the combination product in lieu of the individual monoproducts. Data from secondary endpoints, iTNSS and RQLQ, provide secondary support for efficacy, and the iTNSS data confirm the twice-daily dosing interval as well as the proposed onset of action of 30 minutes. Data from the rTOSS endpoint are also generally supportive of efficacy but are not sufficient to support inclusion of rTOSS data in the label. These conclusions are consistent with the views expressed in the primary clinical review and biostatistics review.

At this time, there are no outstanding clinical issues in terms of efficacy.

8. Safety

The evidence of safety of azelastine/FP is based on the clinical trials outlined in Table 1, as well as the known systemic safety profiles of the commercially marketed azelastine and FP products. This memorandum focuses on the key efficacy trials – 4002, 4004, and 4006 – and the long-term safety trial, 4000. Data from 4001 were also reviewed and were found to be similar to the results of the other trials, but 4001 was not included in the pooled safety database, given the use of different monotherapy comparators. The pooled database includes a total of 1257 patients: 853 patients 12 years and older with SAR treated with azelastine/FP for up to 2 weeks and 404 patients with PAR or VMR treated for up to 12 months.

Safety assessments in the clinical program included adverse events, vital signs, and focused head and neck examinations to evaluate for local toxicity. The design and conduct of the efficacy trials was previously described in Section 7. Trial 4000, the long-term safety study, was an open-label, active controlled trial comparing the safety profiles of azelastine/FP 1 spray per nostril BID to commercial FP 2 sprays per nostril BID. Of note, while the 2-week SAR trials were conducted in the US, the 12-month safety trial was conducted in India. The generalizability of the long-term safety study results was raised as a review issue in the 74-day filing letter. As the nature and frequency of adverse events was fairly similar between the efficacy trials and the safety trial, the clinical review concluded that the results of 4000 were relevant to a US population. Furthermore, local toxicity is the primary AE of interest for this class of drug products and is not expected to vary substantially among different ethnic/racial groups. Overall, the size of the safety database and the safety parameters are considered adequate for characterizing the safety of azelastine/FP.

Deaths, SAEs, and discontinuations due to AEs
There were no deaths in the clinical program. A total of 5 SAEs were reported among patients who received azelastine/FP, and these events did not suggest a specific safety signal. The

discontinuations due to adverse events also did not suggest a new safety signal and the types of AEs cited were similar to the AEs reported during the trials.

Safety concerns of special interest

Local toxicity in the form of nasal septal perforation, ulceration, and epistaxis are safety concerns common to other intranasal products approved for allergic rhinitis. For this reason, the Applicant conducted prospective nasal exams throughout the trials and used a pre-specified grading system for scoring local toxicity. In the azelastine/FP program, there were no reported cases of nasal septal perforation. One case of nasal ulceration was reported in a patient receiving placebo. Epistaxis was reported infrequently and was mostly commonly graded as mild in severity. Other measures of irritation such as mucosal edema, nasal discharge, and mucosal erythema were also similar across treatment arms in the placebo-controlled trials. Similar rates between azelastine/FP and FP were observed in the long-term trial 4000.

Ophthalmic exams for glaucoma and posterior subcapsular cataracts were also prospectively conducted, since these AEs have been associated with other intranasal corticosteroids. Events were rare and similar across treatment arms.

Somnolence and sedation have been previously reported with azelastine and are anticipated with use of azelastine/FP. In the azelastine/FP program, somnolence was reported at a slightly higher rate in groups receiving azelastine/FP (0.7%) or azelastine (0.4%) compared to FP (0.1%) or placebo (0.1%). Paradoxically, somnolence occurred at a higher rate in the FP comparator arm (0.5% vs. 0.2%) compared to azelastine/FP in the long-term trial.

HPA-axis suppression is a potential safety concern described in the package inserts for other intranasal corticosteroids. A formal HPA-axis trial was not conducted for the application. However, the totality of the information provided in the application does not suggest a clinically relevant HPA-axis effect. As mentioned previously, while systemic exposure for FP from the combination is slightly higher than the systemic exposure for commercial FP at the same nominal dose, it falls within the range of systemic exposure observed for the range of doses approved for FP that have been previously shown not to impact the HPA-axis. In addition, the Applicant included serum cortisol measurements in a subset of patients in the long-term safety trial, 4000. Results for azelastine/FP and FP were similar and did not indicate clinically significant changes.

Common adverse events

The overall adverse event profile for azelastine/FP was largely consistent with the safety profiles observed for the corresponding individual monoproducts. The most commonly reported AE was dysgeusia, which is a well-known AE associated with other azelastine products; other common AEs were headache and epistaxis (Table 1).

Table 6 Adverse events ≥1% and occurring at a rate greater than placebo (4002, 4004, 4006)				
Preferred Term	**Azelastine/FP** n=853	**Placebo** n=861	**Azelastine** n=851	**FP** n=846
Any Adverse Event	136 (15.9)	99 (11.5)	124 (14.6)	111 (13.1)
Dysgeusia	30 (3.5)	2 (0.2)	44 (5.2)	4 (0.5)
Headache	18 (2.1)	10 (1.2)	20 (2.4)	20 (2.4)
Epistaxis	16 (1.9)	15 (1.7)	14 (1.6)	14 (1.7)

Safety summary
The placebo-controlled trials 4002, 4004, and 4006, in conjunction with the results of the 12-month trial, 4000, provide adequate support for the safety of azelastine/FP 1 spray per nostril BID for the treatment of the symptoms of allergic rhinitis in patients 12 years and older. Prospective examination for local toxicity did not suggest an additive or synergistic effect of the combination compared to the active comparators. Overall, the nature and frequency of adverse events observed were consistent with the safety profile of the corresponding commercially available monoproducts as described in the current package inserts for each. The conclusions of this memorandum are consistent with the conclusions of the primary clinical review.

There are no outstanding safety issues at this time.

9. Advisory Committee Meeting

As both azelastine and FP are well-established chemical entities, and the proposed indication is consistent with the indication of other intranasal products approved for SAR, no advisory committee meeting was held for this application. A regulatory briefing to discuss the application of the Combination Rule to the azelastine/FP development program was previously held in April 2009 and is summarized in the Background of this memorandum.

10. Pediatrics

(b) (4)

(b) (4)

As with adult SAR patients, the Division believes that the product may be appropriate for a subset of children with SAR whose symptoms are not adequately managed by azelastine or fluticasone propionate nasal spray alone. Furthermore, off-label in pediatric patients is anticipated pending approval in patients 12 years and older, given that Astelin is approved down to the age of 5 years, and FP is approved down to the age of 4 years at total daily doses that correspond to the dosing of azelastine/FP.

(b) (4)

PeRC concurred with the Division's position and recommended that the Applicant be required to conduct pediatric trials in patients 4 to 11 years of age. The request

for waiver for patients <2 years was granted on the basis that the existence of SAR in this age group is uncertain, making studies impossible or highly impractical. The request for waiver in children in 2 to <4 was granted on the basis that the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients in this age range. Of note, FP previously failed to demonstrate efficacy in patients 2 to <4 years in a growth study conducted as part of a Written Request for this moiety.

In response, the Applicant submitted a revised pediatric plan proposing two trials in patients 4 to < 12 years of age. One trial will be (b) (4) the efficacy and safety of azelastine/FP 1 spray per nostril BID (b) (4) in (b) (4) patients with SAR, (b) (4) The other trial will be a 3-month safety trial comparing azelastine/FP 1 spray per nostril BID to active control or placebo in approximately 400 patients with PAR or SAR. The revised pediatric plan was discussed with PeRC and found to be acceptable. The proposed complete study submission date for both trials is June 2014.

11. Other Relevant Regulatory Issues

The Applicant provided a statement indicating the trials were conducted under the principles of Good Clinical Practice (GCP). No financial disclosures were noted for the investigators. Review of the application did not raise any data integrity concerns, and no DSI audit was requested.

As azelastine/FP represents the first fixed-dose intranasal combination product for allergic rhinitis, questions regarding the application of the Combination Rule were raised early in the development program. This issue is discussed in further detail in the preceding Background section.

There are no outstanding regulatory issues at the time of this memorandum.

12. Labeling

The proposed tradename, Dymista®, has been found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

The proposed label is in PLR format. Labeling negotiations are pending at the time of this memorandum. Two issues are worth noting. The first is the issue of the indication wording. While the Applicant has proposed (b) (4) the clinical review has recommended additional language limiting use to patients who require treatment with both azelastine and FP for control of SAR symptoms. This revised indication is consistent with Combination Rule, which states that an appropriate population that requires treatments with all components of the combination should be identified. The revised indication is also intended to address the concern noted earlier that the fixed-dose combination may expose patients to more medication than needed to treat their SAR symptoms. The second major labeling issue pertains to the presentation of clinical trial data in Section 14 of the label. For reasons discussed in Section 7 Clinical Efficacy, the Division has recommended (b) (4)

(b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended action is Approval.

- Risk Benefit Assessment

The risk benefit assessment is favorable for azelastine/FP for the treatment of the symptoms of seasonal allergic rhinitis in patients 12 years and older who require treatment with both components for the relief of symptoms. The application provided replicate, statistically robust evidence of efficacy as measured by total nasal symptom scores and quality-of-life questionnaires. The efficacy data included replicate, statistically significant demonstration of the factorial contribution of each monocomponent to the efficacy of the combination and provided justification for the use of the combination in lieu of the individual components. The application also provided an adequate assessment of safety, demonstrating that the combination of azelastine and FP results in a safety profile that is similar to that of the individual components. Therefore, the risk-benefit assessment supports Approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies are recommended.

- Recommendation for other Postmarketing Requirements and Commitments

The Applicant is required to conduct additional studies in patients 4 to 11 years of age under PREA. The pediatric plan proposes two trials in response to this requirement. The first deferred trial is (b) (4) efficacy and safety trial in SAR patients; the second deferred trial is a 3-month trial in patients with SAR or PAR.

- Recommended Comments to Applicant

No comments.

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/s/

SUSAN L LIMB
04/10/2012