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*APPLICATION NUMBER:*  
**202236Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

Exhibit 1058

## Cross-Discipline Team Leader Review

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

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