CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202236Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	May 1, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-2236
Applicant Name:	Meda Pharmaceuticals, Inc.,
Date of Submission:	April 1, 2011
PDUFA Goal Date:	May 1, 2012 (original goal date was February 1, 2011)
Proprietary Name:	Dymista Nasal Spray
Established Name:	azelastine hydrochloride and fluticasone propionate
Dosage form:	Nasal Spray
Strength:	137 mcg azelastine hydrochloride and 50 mcg of fluticasone propionate per actuation in 137 microliters metered volume
Proposed Indications:	Treatment of symptoms of seasonal allergic rhinitis in patients 12 years of age and older
Action:	Approval

1. Introduction

Meda Pharmaceuticals submitted this 505(b)(2) application for use of Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in adults and adolescents 12 years of age and older. The proposed dose is 1 spray per nostril twice daily, so that the total daily dose is 548 mcg azelastine hydrochloride and 200 mcg fluticasone propionate. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

Meda Pharmaceuticals submitted an amendment on December 7, 2011, containing CMC information on the pharmaceutical characteristics of the novel single ingredient products used as comparators in the pivotal clinical trials, and additional data and methods pertaining to the dose performance and microbial safety of the combination drug product. As these data and information were critical for the interpretation of the clinical trial results and assurance of drug product safety and quality, the amendment was considered to be a major amendment, and the review clock was extended by three months.

2. Background

There are many drugs approved for use in patients with allergic rhinitis (AR) including oral and intranasal H1 antihistamines, intranasal corticosteroids, and the oral leukotriene receptor antagonist montelukast. Both the active ingredients present in Dymista, azelastine hydrochloride and fluticasone propionate, are approved and marketed in the United States as nasal spray formulations for the treatment of AR. In addition, there are

many other intranasal corticosteroids marketed for the treatment of AR in the United States. On approval, Dymista will be the first fixed-dose combination nasal spray product containing an antihistamine and a corticosteroid for the treatment of SAR.

The development of a fixed-dose combination product containing an intranasal corticosteroid and antihistamine raises issues that have not been previously encountered in development programs for single-component nasal spray products, including the ability of clinical studies to satisfy the requirements of the Combination Rule (21CFR 300.50), and to demonstrate clinically meaningful efficacy and safety for the fixed-dose combination product, given the established safety and efficacy of the single ingredient products. Some considerations related to the latter issue are: 1) the identification of an appropriate patient population; 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 single ingredient products that can be used as comparators in factorial-design studies.

Early in development (during the review of IND 77,363), given the complexity surrounding the development of a fixed-dose combination product containing an intranasal corticosteroid and antihistamine for treatment of AR, a Center level Regulatory Briefing on this topic was held on April 17, 2009. Based on the feedback received during this internal discussion, the following decisions were made: 1) the Division will accept a fixed-dose combination product where each single ingredient product present in the fixed-dose combination product treats the same symptoms of AR; 2) the evaluation of total nasal symptom score as the primary endpoint is acceptable for comparing the combination product to the single ingredient products; 3) the contribution of each active component in the fixed-dose combination product must be demonstrated through clinical studies; 4) there should be no pharmaceutical differences between the fixed-dose combination product and the single ingredient products used in pivotal clinical studies; 5) the demonstration of a statistically significant difference between the fixed-dose combination product and each of its single ingredients is accepted as evidence of a patient population requiring concurrent therapy, provided that the effect sizes separating the fixed-dose combination product and each of its single ingredients are of reasonable magnitude and each single ingredient product also demonstrates superiority to placebo; and 6) statistical significance driven by a large sample size with a marginal treatment effect is not adequate, and treatment effect size should be defined a priori and comparable to the effect size already determined to be acceptable for the single ingredient products.

The Division communicated the above issues and discussed the pathway forward with Meda Pharmaceuticals in a teleconference held on April 23, 2009. During the teleconference the Division reiterated the need for demonstrating that there were no pharmaceutical differences between the combination product and each of the single ingredient comparators to be used in pivotal clinical trials. Due to the pharmaceutical differences between Dymista and the corresponding commercial single ingredient products containing azelastine hydrochloride and fluticasone propionate, Meda Pharmaceuticals was advised to develop single ingredient comparator products for the clinical development program. Since the single ingredient comparator products would be

new products, each would require demonstration of safety and efficacy as compared to placebo. Subsequently, Meda Pharmaceuticals developed appropriate single ingredient comparator products and conducted an appropriate clinical development program that is the subject of this review.

3. Chemistry, Manufacturing, and Controls

The drug substances azelastine hydrochloride and fluticasone propionate are known active ingredients that are already approved in commercial inhalation and nasal spray products as mentioned above. Dymista Nasal Spray is a metered dose spray pump unit containing a suspension formulation of 0.1% azelastine hydrochloride and 0.037% fluticasone propionate and compendial excipients. The commercial unit has a fill weight of 23 gm and delivers a minimum 120 sprays after priming. The product does not have a dose counter. After priming, each metered spray delivers 0.137 mL volume of suspension containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate from the nose piece.

The drug substance azelastine hydrochloride is manufactured by (b) (4) and fluticasone propionate is manufactured by (b) (4) The drug product is manufactured by Cipla in Goa, India. Each manufacturing and testing facility associated with this application has acceptable EER status. The submitted stability data support drug product storage at the room temperature and an expiry period of 24 months.

Initial review of the CMC data noted deficiencies in the proposed specifications, analytical methods, and stability data for the drug product. In addition, it was noted that the actuator detached easily from the glass vial during removal of the dust cap. During the review cycle Meda Pharmaceuticals adequately addressed all CMC deficiencies and proposed new acceptance criteria for spray weight, spray content uniformity, droplet size distribution, and the microscopic method for particle size distribution. Manufacturing changes were also implemented to seat the actuator more securely on the pump.

Given the issues and complexities of developing a fixed-dose nasal spray combination product (discussed in section 2 above), characterization of the single ingredient products and their comparison to the fixed-dose combination product for potential pharmaceutical interactions was an important part of the CMC review for this application. While azelastine hydrochloride and fluticasone propionate are marketed as individual products, the formulation of the commercially available products differs from the formulation of the proposed fixed-dose combination product. Therefore, Meda Pharmaceuticals developed novel azelastine hydrochloride 0.1% nasal spray and fluticasone propionate 0.037% nasal spray single ingredient products specifically for use in the pivotal clinical trials. As mentioned in Section 1 above, complete CMC information for the single ingredient comparator products was submitted later in the review cycle, leading to the extension of the PDUFA clock. On review of the data for the single ingredient products, it was found that there were some minor differences (b) (4)

(b) (4) but the overall dose performance results are considered to be within the acceptable range (variation of NMT (b) (4)) compared to the combination product. Based on the in vitro data, it was concluded that there are no significant pharmaceutical differences between the fixed-dose combination product and the single-ingredient component products, and no interactions between the active ingredients in the fixed-dose combination product, which would potentially impact the interpretation of the clinical study results.

4. Nonclinical Pharmacology and Toxicology

The nonclinical program for Dymista is based upon completed toxicology programs conducted for the individual active moieties azelastine hydrochloride and fluticasone propionate. These were previously reviewed under the NDAs for these products and were found to be acceptable. To support this application, Meda Pharmaceuticals conducted 14-day intranasal toxicology studies in rats and dogs and a 3-month intranasal toxicology study in rats with azelastine hydrochloride and fluticasone propionate administered as a combination product. These toxicology studies did not indicate any potential additive or synergistic toxic effects of the combination.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for azelastine hydrochloride and fluticasone propionate were addressed in the original NDAs for these products. The clinical pharmacology program for this application included two single-dose, relative bioavailability studies in healthy volunteers to assess for potential drug-drug interactions and assess systemic exposure. These studies demonstrated that co-administration of azelastine hydrochloride and fluticasone propionate does not affect the systemic exposure of either. Systemic exposure for azelastine from Dymista is within ±20% of that associated with the commercially marketed azelastine product, Astelin. The systemic exposure for fluticasone propionate from Dymista is 44 to 61% higher than exposure from a commercially marketed, generic fluticasone propionate nasal spray product at the same nominal dose. However, the systemic exposure of fluticasone propionate from Dymista is below the systemic exposure from higher doses of commercially marketed fluticasone propionate nasal spray (Flonase 200 mcg once daily or 400 mcg twice daily), which have been reported to have no effect on adrenal responses as is described in the current Flonase package insert. The information regarding relative systemic exposures suggests that the higher systemic exposure observed for fluticasone propionate from Dymista is not likely to pose new systemic safety concerns. Therefore, a separate HPA-axis safety study was not deemed to be necessary for Dymista.

6. Clinical Microbiology

The final product is not sterile (b) (4) (b) (4) which is acceptable for a nasal spray product. Data for the (b) (4) proposed microbial safety controls were reviewed and additional controls for the absence of *B. cepacia* were requested by the Microbiology

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