CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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)

[redacted] but the overall dose performance results are considered to be within the acceptable range (variation of NMT [redacted]) 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 [redacted] which is acceptable for a nasal spray product. Data for the [redacted] proposed microbial safety controls were reviewed and additional controls for the absence of *B. cepacia* were requested by the Microbiology

review team. The new method and revised microbial controls submitted in the NDA amendment dated December 7, 2012, are considered adequate to assure drug product safety from the Microbiology perspective.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies

ID Year *	**Study type**	**Study duration**	**Patient Age, yr**	**Treatment groups#**	**N†**	**Primary efficacy variable**	**Countries**
4001 2008	Efficacy and Safety in SAR	2 week	12 - 75	Dymista 137/50 mcg BID Astelin 137 mcg BID Flonase (generic) 50 mcg BID Placebo	153 153 153 151	Reflective total nasal symptom score over 2 wks	US [Texas]
4002 2008	Efficacy and Safety in SAR	2 week	12 - 77	Dymista 137/50 mcg BID Azelastine 137 mcg BID Fluticasone 50 mcg BID Placebo	207 208 207 210	Reflective total nasal symptom score over 2 wks	US [Various States]
4004 2008	Efficacy and Safety in SAR	2 week	12 - 77	Dymista 137/50 mcg BID Azelastine 137 mcg BID Fluticasone 50 mcg BID Placebo	195 194 189 201	Reflective total nasal symptom score over 2 wks	US [Various States]
4006 2009	Efficacy and Safety in SAR	2 week	12 - 83	Dymista 137/50 mcg BID Azelastine 137 mcg BID Fluticasone 50 mcg BID Placebo	451 449 450 451	Reflective total nasal symptom score over 2 wks	US [Various States]
4000 2009	Safety in PAR and VMR	52 week	12 - 73	Dymista 137/50 mcg BID Flonase (generic) 50 mcg BID	405 207	Safety study	India

*Year study subject enrollment ended
All treatment administered as 1 spray in each nostril BID except in studies 4001 and 4000 that used commercial single ingredient commercial products where Flonase was administered as 2 sprays in each nostril BID
Note: All doses are from the end of the nose piece of the metered-dose spray pump unit
† Number randomized

b. Design and conduct of the studies

All efficacy and safety studies (4001, 4002, 4004, and 4006) were randomized, double-blind, placebo-controlled, and parallel-group in design and conducted in patients 12 years of age and older with SAR. For the SAR study 4001, Texas Mountain Cedar was the specified allergen. The studies had a 1-week single-blind placebo run-in period followed by a double-blind treatment period of 2 weeks with full factorial design using four treatment arms that allowed comparison of Dymista with each single ingredient comparator product, comparison of each single ingredient product with placebo, and comparison of Dymista with placebo (Table 1). The primary efficacy endpoint for all studies was the change from baseline in average morning and evening reflective total

nasal symptom scores (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) collected daily and averaged over 2 weeks of treatment. Some key secondary efficacy variables included: (1) the instantaneous recording of the same four symptoms (iTNSS) for all studies, (2) reflective and instantaneous total ocular symptom score (rTOSS or iTOSS: sum of ocular itching, tearing, and redness; each scored on 0-3 scale), and (3) the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for patients 18 years of age and older. Safety assessments included recording of adverse events, vital signs, and focused nasal examinations.

Study 4000 was a 52-week dedicated safety study that compared Dymista to commercially available generic Flonase. Safety assessments included recording of adverse events, vital signs, physical examinations including focused nasal examinations, eye examination, ECG, and clinical laboratory measurements. In additional an evaluation of the hypothalamic-pituitary-adrenal (HPA) axis by measurement of serum cortisol was conducted in a subset of patients at some selected sites.

The design and conduct of efficacy and safety studies were typical of an AR program. There were two issues in the clinical program that warrant further comments, as follows.

First, in study 4001 commercially available Astelin and a generic Flonase were used as single ingredient comparators. Since there are known pharmaceutical differences between Dymista and the single ingredient comparators, the results of this study are not adequate to show contribution of each active component in the combination product Dymista. Nevertheless, study 4001 provides supportive information. Note that there are three other studies (4002, 4004, and 4006) that used appropriate single ingredient comparator products that are not pharmaceutically different than Dymista.

Second, in the SAR study 4001, the allergen was specified as Texas Mountain Cedar. Mountain Cedar produces intense symptoms and clinical studies conducted in SAR patients allergic to this allergen may show a larger treatment effect size compared to clinical studies conducted in SAR patients allergic to heterogeneous seasonal allergens. Use of a Texas Mountain Cedar-sensitive SAR patient population is acceptable because demonstration of efficacy in one allergen-sensitive SAR patient group is expected to support efficacy in other allergen sensitive patient groups in SAR since the underlying pathophysiology of SAR is similar across allergens. However, the possible inflation of treatment effect size is taken in consideration with the other limitations to the relevance of study 4001 as stated above.

c. Efficacy findings and conclusions

The submitted studies support efficacy of Dymista Nasal Spray (azelastine hydrochloride 137 mcg and fluticasone propionate 50 mcg) at a dose of 1 spray per nostril twice daily for daily in adult and adolescent patients with SAR 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

Formal dose ranging studies with Dymista were not conducted. Dose selection for each component of azelastine hydrochloride and fluticasone propionate was based on the approved doses of each of these products and supported by the submitted efficacy and safety data (Table 1). This is acceptable because a combination product such as Dymista is a product of convenience for patients who require treatment with both azelastine hydrochloride and fluticasone propionate.

In studies 4001, 4002, 4004, and 4006, Dymista demonstrated statistically significant differences from each single ingredient comparator product in the primary efficacy endpoint of rTNSS and also for iTNSS (Table 2). The only borderline result was the comparison of Dymista to fluticasone propionate for rTNSS in study 4004 (p=0.06), but in the same study the results were statistically significant for iTNSS. Study 4001 is considered supportive for reasons stated above (use of commercially available Astelin and a generic Flonase as single ingredient comparators). The other three studies considered pivotal (4002, 4004, and 4006) used appropriate single ingredient comparator products. The two single ingredient products specifically formulated for comparing to Dymista demonstrated statistically significant differences from placebo in studies 4002, 4004, and 4006 (raw data shown in Table 2, p<0.001). The data overall provide evidence of the contribution of each active component in the combination product Dymista, and also show a clinically meaningful efficacy advantage for the combination product Dymista over the single ingredient products that were also efficacious in SAR. The magnitude of the treatment differences between Dymista and each active single ingredient comparator product were reasonable and comparable to the differences observed for nasal antihistamines and nasal corticosteroids in other clinical programs for SAR. Statistical significance for the differences between Dymista and the single ingredient comparator products were achieved in all studies. All studies, except 4006, had sample sizes comparable to those used in the clinical studies that supported approval of these single ingredient products. The sample size used in study 4006 was substantially larger, but this study provides point estimates for the treatment differences with more precision than the smaller studies. The smaller studies 4002 and 4004 provide necessary and adequate evidence of efficacy, and study 4006 provides additional confirmatory evidence.

Table 2. Change from baseline in nasal symptoms scores rTNSS and iTNSS *

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from Dymista LS mean	95% CI	P value
SAR Study 4001							
rTNSS	Dymista 137/50 mcg	153	18.6	-5.4			
	Astelin 137 mcg	152	17.9	-3.4	-2.1	(-3.0, -1.2)	<0.001
	Flonase 50 mcg	151	18.1	-4.0	-1.4	(-2.4, -0.5)	0.003
	Placebo	150	18.5	-2.3	-3.1	(-4.0, -2.2)	<0.001
iTNSS	Dymista 137/50 mcg	153	17.1	-4.5			
	Astelin 137 mcg	152	16.5	-3.0	-1.5	(-2.4, -0.6)	0.002
	Flonase 50 mcg	151	16.8	-3.6	-0.9	(-1.8, -0.1)	0.066
	Placebo	150	17.5	-1.7	-2.8	(-3.7, -1.9)	<0.001
SAR Study 4002							
rTNSS	Dymista 137/50 mcg	207	18.3	-5.6			
	Azelastine 137 mcg	208	18.3	-4.3	-1.4	(-2.2, -0.5)	0.002

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from Dymista LS mean	95% CI	P value
	Fluticasone 50 mcg	207	18.2	-4.7	-1.0	(-1.8, -0.2)	0.022
	Placebo	209	18.6	-2.9	-2.7	(-3.5, -1.9)	<0.001
iTNSS	Dymista 137/50 mcg	207	17.2	-5.2			
	Azelastine 137 mcg	208	16.8	-3.9	-1.3	(-2.1, -0.5)	0.002
	Fluticasone 50 mcg	207	16.8	-4.5	-0.7	(-1.5, 0.2)	0.116
	Placebo	209	17.3	-2.7	-2.6	(-3.4, -1.8)	<0.001
SAR Study 4004							
rTNSS	Dymista 137/50 mcg	193	18.3	-5.5			
	Azelastine 137 mcg	193	18.5	-4.5	-1.0	(-1.9, -0.1)	0.030
	Fluticasone 50 mcg	188	18.6	-4.7	-0.9	(-1.8, 0.0)	0.060
	Placebo	199	18.2	-3.1	-2.4	(-3.2, -1.6)	<0.001
iTNSS	Dymista 137/50 mcg	193	17.2	-5.2			
	Azelastine 137 mcg	194	17.3	-4.1	-1.1	(-1.9, -0.2)	0.020
	Fluticasone 50 mcg	188	17.2	-4.4	-0.8	(-1.7, 0.1)	0.084
	Placebo	199	16.8	-2.6	-2.6	(-3.4, -1.8)	<0.001
SAR Study 4006							
rTNSS	Dymista 137/50 mcg	448	19.3	-5.6			
	Azelastine 137 mcg	443	19.5	-4.8	-0.8	(-1.3, -0.2)	0.012
	Fluticasone 50 mcg	450	19.4	-4.9	-0.6	(-1.2, -0.1)	0.030
	Placebo	448	19.4	-3.4	-2.2	(-2.7, -1.6)	<0.001
iTNSS	Dymista 137/50 mcg	448	17.9	-5.0			
	Azelastine 137 mcg	445	18.0	-4.3	-0.7	(-1.3, -0.1)	0.019
	Fluticasone 50 mcg	450	17.8	-4.7	-0.3	(-0.9, 0.3)	0.345
	Placebo	448	17.9	-3.1	-1.9	(-2.5, -1.4)	<0.001

* Subject-rated rated AM and PM reflective or instantaneous total nasal symptom scores (rTNSS or iTNSS) (maximum score = 24) averaged over the 2-week treatment period. Analyses used raw scores.

† Treatment administered as 1 spray in each nostril BID except in study 4001 that used commercial single ingredient commercial products where Flonase was administered as 2 sprays in each nostril BID

Note: All doses are from the end of the nose piece of the metered-dose spray pump unit

(b) (4)

Meda Pharmaceuticals included the RQLQ in the studies to support a labeling claim. The RQLQ is a 28-item disease specific (allergic rhinitis) quality of life instrument with seven domains (activity limitations, sleep problems, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function). Patients treated with Dymista demonstrated statistically significant improvements in RQLQ compared to placebo, but not compared to the single ingredient products (Table 4). The treatment group differences for Dymista compared to placebo in each of the studies crossed 0.5, which is considered to be the MID (minimum important difference). The results comparing Dymista to placebo will be described in the product label. This will be consistent with similar labeling language that has been permitted for inhaled combination products for the treatment of patients with asthma.

Table 4. Change from baseline in RQLQ over 2 weeks (ITT population, excluding patients with missing baseline value) *

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from Dymista LS mean	95% CI	P value
SAR Study 4002							
RQLQ	Dymista 137/50 mcg	176	3.9	-1.6			
	Azelastine 137 mcg	174	3.8	-1.4	-0.3	(-0.5, 0.0)	0.029
	Fluticasone 50 mcg	184	3.8	-1.6	-0.0	(-0.4, 0.2)	0.907
	Placebo	169	3.9	-0.9	-0.8	(-1.1, -0.6)	<0.001
SAR Study 4004							
RQLQ	Dymista 137/50 mcg	176	3.8	-1.7			
	Azelastine 137 mcg	172	3.8	-1.4	-0.3	(-0.5, 0.0)	0.031
	Fluticasone 50 mcg	169	3.8	-1.5	-0.2	(-0.5, 0.1)	0.123
	Placebo	171	3.9	-1.0	-0.7	(-1.0, -0.5)	<0.001
SAR Study 4006							
RQLQ	Dymista 137/50 mcg	381	3.9	-1.6			
	Azelastine 137 mcg	394	3.9	-1.4	-0.2	(-0.3, 0.0)	0.043
	Fluticasone 50 mcg	384	3.9	-1.6	-0.0	(-0.2, 0.1)	0.629
	Placebo	393	3.9	-1.0	-0.6	(-0.7, -0.4)	<0.001

* Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (28 items in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) evaluated on a 7-

Treatments †	n	Baseline LS mean	Change from baseline	Difference from Dymista LS mean	95% CI	P value
point scale where 0=no impairment and 6=maximum impairment), which was administered to patients 18 years of age and older. An overall RQLQ score is calculated from the mean of all items in the instrument. † Treatment administered as 1 spray in each nostril BID Note: All doses are from the end of the nose piece of the metered-dose spray pump unit						

To support an onset of action claim, Meda Pharmaceuticals did not conduct dedicated studies such as an "allergen chamber" study or "day-in-the-park" study that provides pharmacodynamic onset of action. Instead, onset of action for Dymista was assessed by frequent recording of iTNSS in the SAR studies after the first dose. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment and placebo in the efficacy measure is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful. The pivotal SAR studies provide a more clinically meaningful assessment of onset of action than pharmacodynamic "allergen chamber" and "day-in-the-park" type studies would. The data submitted support an onset of action of 30 minutes for Dymista.

8. Safety

a. Safety database

The safety assessment of Dymista is primarily based on studies listed in Table 1, as well as the known safety profiles of the commercially marketed single ingredient nasal spray products containing azelastine hydrochloride and fluticasone propionate. The overall safety database for Dymista was adequate.

Two separate pooling of 2-week studies were done for assessment of safety. One pooling included studies 4001, 4002, 4004, and 4006, and the second pooling excluded study 4001 (Table 1). In the product label, data from pooled studies 4002, 4004, and 4006 are reported. Results of study 4001 are excluded because this study included single ingredient comparators different from the other three studies. Including all studies in product label would necessitate listing multiple single ingredient product comparators that would increase complexity, but would not provide additional useful information.

b. Safety findings and conclusion

The submitted data support the safety of Dymista Nasal Aerosol in patients 12 years of age and older. There were no deaths in the clinical program. Serious adverse events were few, did not appear to be related to Dymista, and did not suggest a new safety signal. The discontinuations due to adverse events also did not suggest a new safety signal for Dymista. Common adverse events in Dymista treated patients were dysgeusia, headache, and epistaxis. These are typical adverse events seen in SAR studies using nasal spray products containing antihistamines or corticosteroids.

Focused nasal examinations were conducted in all clinical studies because local nasal toxicities such as nasal septal perforation, nasal mucosal ulceration, and epistaxis are

safety concerns of interest for nasal spray products. In the clinical program for Dymista there were no septal perforations seen. There was one report of nasal ulceration in a patient on placebo treatment. There were few cases of epistaxis, but they were generally mild in severity. Overall, these findings do not raise any safety concerns for Dymista.

Ophthalmologic examination was done in the Dymista clinical studies. Events of interest, such as increased intraocular pressure and cataracts, were rare and similar across treatment arms.

HPA axis effect was not formally assessed for Dymista in a dedicated study. The totality of the information provided by Meda Pharmaceuticals does not suggest a clinically relevant HPA-axis effect for Dymista. As mentioned previously, while systemic exposure for fluticasone propionate from Dymista is slightly higher than that for commercial Flonase at the same nominal dose, it falls within the range of systemic exposure observed for approved doses of Flonase that have been previously shown not to impact the HPA-axis. In addition, Meda Pharmaceuticals included serum cortisol measurements in a subset of patients in the long-term safety study 4000. Results for Dymista and Flonase were similar in the study and did not indicate clinically significant changes.

A linear growth study with Dymista is not necessary because a growth study has been conducted with another product containing fluticasone propionate. Comparative systemic exposure data for fluticasone propionate from Dymista compared to other products do not raise specific concerns about growth suppression with Dymista, however, the package insert includes class labeling describing the association between intranasal corticosteroids and the reduction of growth velocity.

c. REMS/RiskMAP

There are no substantial safety concerns that would require a REMS or RiskMAP. Other nasal spray products containing single ingredient azelastine hydrochloride or fluticasone propionate also do not have a REMS or RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Both azelastine hydrochloride and fluticasone propionate are not new molecular entities. Nasal spray products containing both these active moieties are well studied for AR, and the efficacy and safety of these single entity products for AR are well known. The efficacy and safety findings seen in the clinical program for Dymista were obvious. There were no issues that warrant discussion at an advisory committee meeting. A CDER regulatory briefing addressing issues relevant to the development of a fixed-dose combination product containing an intranasal corticosteroid and antihistamine for treatment of AR was held on April 17, 2009 as discussed in Section 2 above.

10. Pediatric

[redacted] As is the case for patients 12 years of age and older, Dymista may be appropriate for younger patients who would require treatment with both azelastine hydrochloride and fluticasone propionate. Furthermore, single ingredient Astelin (azelastine hydrochloride) is approved down to 5 years of age, and single ingredient Flonase (fluticasone propionate) is approved down to 4 years of age at daily doses that correspond to the dosing of Dymista.

The application was reviewed by the FDA Pediatric Review Committee (PeRC) on November 30, 2011. PeRC also concluded that [redacted] and recommended that Meda Pharmaceuticals be required to conduct studies in patients 4 to 11 years of age. Waiver for patients below 2 years was granted on the basis that the existence of SAR in this age group is uncertain, making studies for Dymista impossible or highly impractical. The lower age bound of 2 years is typical for a nasal corticosteroid and the Division has not asked that drugs of this class be studied in children younger than 2 years. The Division has historically taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature supporting the lower age bound (J Allergy Clin Immunol 2000, 106:832). For children younger than 2 years, nasal corticosteroids are not an optimum choice because of possible nasal and systemic adverse effects. Waiver for patients 2 to 4 years was granted on the basis that Dymista fails to represent a meaningful benefit over existing therapies and is unlikely to be used in a substantial number of patients in this age range.

Meda Pharmaceuticals later submitted a revised pediatric plan proposing two studies in patients 4 to <12 years of age. The first study will be [redacted] efficacy and safety of Dymista 1 spray per nostril BID [redacted] in [redacted] patients with SAR, [redacted]. The second study will be a 3-month safety study comparing Dymista 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 on March 21, 2012, and found to be acceptable. The proposed complete study report submission date for both studies is June 2014.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audit was not conducted for this application because single ingredient products containing both active moieties present in Dymista are approved for SAR, and no evidence of a disproportionate center response for efficacy or safety was seen in the Dymista clinical program. During review of this application, the review team did not

identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There was no investigator with significant equity interest in Meda Pharmaceuticals.

c. Others

There are no outstanding issues with consult reviews received from DDMAC and other groups within the Agency.

12. Labeling

a. Proprietary Name

Meda Pharmaceuticals submitted Dymista as the proposed proprietary name, which was found to be acceptable by the DMEPA.

b. Physician Labeling

Meda Pharmaceuticals submitted a label in the Physician Labeling Rule format that generally contains information consistent with the product labels of other nasal spray products containing azelastine hydrochloride and fluticasone propionate. The label was reviewed by various disciplines of this Division and by DDMAC. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DDMAC, and DMEPA, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The Patient Information and Instructions for Use was reviewed by various disciplines of this Division, and DMPP, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Meda Pharmaceuticals has submitted adequate data to support approval of Dymista Nasal Spray (azelastine hydrochloride 137 mcg and fluticasone propionate 50 mcg) at a dose of 1 spray per nostril twice daily for adult and adolescent patients 12 years of age and older with SAR who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief. The action on this application will be Approval.

b. Risk Benefit Assessment

The risk and benefit assessment of Dymista supports its approval for relief of symptoms of SAR in patients 12 years of age and older. There were no unique safety findings of

concern with Dymista. Safety findings with Dymista were consistent with nasal spray products containing the active moieties azelastine hydrochloride and fluticasone propionate that are present in Dymista. The efficacy data provide evidence of the contribution of each active component in the combination product Dymista, and also show a clinically meaningful efficacy advantage of the combination product Dymista over the single ingredient products that were also efficacious in SAR. The magnitude of the treatment differences between Dymista and each active single ingredient comparator product were reasonable and comparable to the differences observed for nasal antihistamines and nasal corticosteroids in other clinical programs for SAR.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

The pediatric studies discussed in Section 10 will be required post-marketing studies.

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/s/

BADRUL A CHOWDHURY
05/01/2012
Div Dir Summary Review