CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	August 31, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-371
Applicant Name:	MEDA Pharmaceuticals
Date of Submission:	August 1, 2008
PDUFA Goal Date:	September 1, 2009 (original goal date was June 1, 2009)
Proprietary Name:	Astepro Nasal Spray 0.15%
Established Name:	Azelastine hydrochloride
Dosage form:	Nasal Spray
Strength:	205.5 mcg in each 0.137 mL spray
Proposed Indications:	Treatment of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis
Action:	Approval

1. Introduction

MEDA Pharmaceuticals submitted this 505(b)(1) application for use of Astepro (azelastine hydrochloride) Nasal Spray 0.15% for relief of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 12 years of age and older. The proposed dose is 1 or 2 sprays per nostril twice daily or 2 sprays once daily for patients with SAR, and 2 sprays per nostril twice daily for patient with PAR. The proposed once daily dosing regimen was not supported by data submitted with the original application. To support the once daily dosing regimen in patients with SAR the applicant submitted results of an additional clinical study toward the end of the review cycle that resulted in extension of the PDUFA goal date by 3 months. 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.

2. Background

There are many drugs approved for use in patients with allergic rhinitis, most of them belonging to classes of H1 receptor antagonists or antihistamines, nasal corticosteroids, and the leukotriene receptor antagonist montelukast. Antihistamines are also used for treatment of other allergic diseases, such as allergic conjunctivitis, and urticaria. Azelastine is an antagonist of the histamine H1 receptor. The applicant has an ophthalmic formulation of azelastine marketed in the United States under the trade name Optivar, and two nasal spray formulations of azelastine marketed in the United States under the trade name Astelin and Astepro. Astelin was approved in November 1996 for SAR, and in September 2000 for vasomotor rhinitis (VMR). Astepro was approved in October 2008 for SAR. The dosing regimens of both Astelin and Astepro are 1 or 2

sprays per nostril twice daily. Both Astelin and Astepro are 0.1% formulations of azelastine hydrochloride. The major difference between Astelin and Astepro is that the latter contains two additional excipients, sucralose and sorbitol, added to give the formulation a sweet taste with the intent that the sweet taste will mask the distinctive bitter taste of azelastine. Astelin has a high frequency of reports of a distinctive bitter taste that has apparently limited patient acceptance. The applicant developed the higher 0.15% formulation of Astepro with the intent of demonstrating improved efficacy over the currently marked 0.1% formulations of Astelin and Astepro, to gain the PAR indication, and to support a once daily dosing recommendation for the SAR indication.

3. Chemistry, Manufacturing, and Controls

The drug substance azelastine hydrochloride is a well known compound that is already approved in commercial ophthalmic and nasal spray products as mentioned above. Astepro 0.15% is a 0.15% w/v solution of azelastine hydrochloride adjusted to a target pH of 5.0 to 5.4. The major difference between Astelin and Astepro is that the latter contains two additional excipients, sucralose at (b) (4) and sorbitol at (b) (4) These two excipients are added to give the formulation a sweet taste with the intent that the sweet taste will mask the distinctive bitter taste of azelastine. The drug substance source, manufacturing, and specifications are the same for Astelin, Astepro 0.1%, and Astepro 0.15%. Astepro 0.15% delivers 205.5 mcg azelastine per 0.137 mL actuation, as compared to the currently marketed Astepro 0.1%, which delivers 137 mcg azelastine hydrochloride per 0.137 mL actuation. The container and pump closure system used in Astelin and both strength Astepro products are similar. The drug product specifications of all are also similar. All manufacturing and testing facilities associated with this application have acceptable EER status. The submitted stability data indicate that Astepro can be stored at room temperature with an expiry of 24 months.

4. Nonclinical Pharmacology and Toxicology

A full toxicology assessment for azelastine was submitted previously and reviewed under NDA 20-114 for Astelin, and toxicology assessment to support the two additional excipients present in Astepro was submitted and previously reviewed under NDA 22-203. To support azelastine nasal spray 0.15%, the applicant submitted results from an adequate bridging toxicology program comparing the various nasal spray products.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for azelastine hydrochloride were addressed in the original NDAs for Astelin and Astepro. No new clinical pharmacology data were submitted with this application.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective. The drug product contains benzalkonium chloride as an (b) (4).

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application was relatively large because of the diverse nature of the claims – SAR indication, PAR indication, and a new once daily dosing regimen. 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. Pivotal clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Submitted with the original application:							
Seasonal Allergic Rhinitis (SAR) Studies							
MP 433	Efficacy and safety Comparative	2 weeks	13-83	Ap 0.15% 2 sp BID Ap 0.15% 2 sp QDAM As 0.1% 2 sp BID Pbo 2 sp BID	153 158 153 153	2006	USA
MP 438	Efficacy and safety Comparative	2 weeks	12-79	Ap 0.15% 2 sp BID Ap 0.10% 2 sp BID Pbo 2 sp BID	177 169 177	2007	USA
MP 439	Efficacy and safety	2 weeks	12-78	Ap 0.15% 2 sp QD Pbo 2 sp QD	238 242	2007	USA
MP 440	Efficacy and safety	2 weeks	12-81	Ap 0.15% 2 sp QD Pbo 2 sp QD	266 266	2008	USA
Perennial Allergic Rhinitis (PAR) Studies							
MP 434	Efficacy and safety Comparative	4 weeks	12-84	Ap 0.15% 2 sp BID Ap 0.10% 2 sp BID Pbo 2 sp BID	192 194 192	2007	USA
MP 435	Efficacy and safety	4 weeks	12-76	Ap 0.15% 2 sp QDAM Ap 0.15% 2 sp QDPM Pbo QD AM PBO QD PM	53 50 23 27	2007	USA
MP 436	Long-term safety	12 month	12-84	Ap 0.15% BID MF 2 sp QD	466 237	2008	USA
Submitted within review period to further support QD dosing:							
Seasonal Allergic Rhinitis (SAR) Study							
MP 443	Efficacy and safety	2 weeks	12-75	Ap 0.15% 2 sp QDAM	251	2009	USA
				Pbo QDAM	254		

* Ap 0.15 % = Astepro 0.15 % Nasal Spray; Ap 0.10 % = Astepro 0.10 % Nasal Spray; As 0.1% = Astelin 0.1% Nasal Spray; Pbo = Placebo Nasal spray; MF = mometasone furoate nasal spray (Nasonex);
# Year study subject enrollment ended

b. Design and conduct of the studies

The studies had many similarities in design and conduct. The descriptions of studies are grouped by the patient population studied.

Seasonal Allergic Rhinitis (SAR) Studies:

Studies 433, 438, 439, 440, and 443 were randomized, double-blind, placebo-controlled, parallel-group design study conducted in patients 12 years of age and older with SAR. For studies 440 and 443 the allergen was specified as Texas Mountain Cedar. The studies had a 7 day placebo run-in period followed by a 2 week double-blind treatment period. The primary efficacy endpoint was the change from baseline in morning plus 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 averaged over 2 weeks of treatment. Secondary efficacy variables included the instantaneous recording of the same four symptoms (iTNSS) and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety assessments included recording of adverse events, vital signs, physical examinations, and clinical laboratory measurements.

Perennial Allergic Rhinitis (PAR) Studies:

Studies 434 and 435 were similar in design to the SAR studies except that the study duration was 4 weeks. Efficacy and safety variables were similar. Study 435 was a smaller proof of concept study testing a once daily dosing regimen in PAR patients. Results of study 435 are not presented in this review.

Study 436 was an open-label, active controlled long-term study to evaluate the long-term safety of Astepro 0.15%. Efficacy was assessed by RQLQ. Compliance was assessed by recording of doses in diary and bottle weights.

c. Efficacy findings and conclusions

The submitted clinical studies, along with the known efficacy of Astepro 0.1% and Astelin, are adequate to support the efficacy of Astepro 0.15% for relief of symptoms of SAR in patients 12 years of age and older at doses of 1 or 2 sprays per nostril twice daily or 2 sprays per nostril once daily, and in PAR in patients 12 years of age and older at a dose of 2 sprays per nostril twice daily. The submitted data also support approval of Astepro 0.15% as a higher dosage strength in addition to the already approved Astepro 0.1%. In the subsequent sections three areas are discussed - the SAR indication, the PAR indication, and the rationale of approval of Astepro 0.15% in addition to the already approved Astepro 0.1%. The results of the studies that support these discussions are presented in Table 2 and Table 3.

Table 2. SAR studies, Mean change from baseline in selective efficacy variables *

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from placebo LS mean	95% CI	P value
Study MP 433 [Trial 2 in product label]							
rTNSS	Ap 0.15% 2 sp BID	153	18.2	-4.3	-1.2	-2.1, -0.3	0.01
	Ap 0.15% 2 sp QDAM	158	18.6	-3.9	-0.8	-1.7, 0.1	0.08
	As 2 sp BID	153	17.9	-3.9	-0.9	-1.8, 0.1	0.07
	Pbo 2 sp BID	153	18.1	-3.0			
iTNSS	Ap 0.15% 2 sp BID	153	17.3	-3.7	-0.7	-1.7, 0.3	0.14
	Ap 0.15% 2 sp QDAM	158	18.0	-3.4	-0.4	-1.3, 0.6	0.49
	As 2 sp BID	153	17.1	-3.9	-0.9	-1.8, 0.1	0.08
	Pbo 2 sp BID	153	17.2	-3.0			
Study MP 438 [Trial 3 in product label]							
rTNSS	Ap 0.15% 2 sp BID	177	17.7	-5.1	-3.0	-3.9, -2.1	<0.001
	Ap 0.10% 2 sp BID	169	18.2	-4.2	-2.1	-3.0, -1.2	<0.001
	Pbo 2 sp BID	177	17.7	-2.1			
iTNSS	Ap 0.15% 2 sp BID	177	16.3	-4.2	-2.6	-3.5, -1.7	<0.001
	Ap 0.10% 2 sp BID	169	17.1	-3.4	-1.8	-2.7, -0.9	<0.001
	Pbo 2 sp BID	177	16.4	-1.6			
Study MP 439 [Trial 4 in product label]							
rTNSS	Ap 0.15% 2 sp QD	238	17.4	-3.4	-1.0	-1.7, -0.3	0.008
	Pbo 2 sp QD	242	17.4	-2.4			
iTNSS	Ap 0.15% 2 sp QD	238	8.1	-1.3	-0.2	-0.6, 0.1	0.147
	Pbo 2 sp QD	242	8.3	-1.1			
Study MP 440 – Texas Mountain Cedar [Trial 5 in product label]							
rTNSS	Ap 0.15% 2 sp QD	266	18.5	-3.3	-1.4	-2.1, -0.8	<0.001
	Pbo 2 sp QD	266	18.0	-1.9			
iTNSS	Ap 0.15% 2 sp QD	266	8.7	-1.4	-0.7	-1.0, -0.4	<0.001
	Pbo 2 sp QD	266	8.3	-0.7			
Study MP 443 – Texas Mountain Cedar [Trial 6 in product label]							
rTNSS	Ap 0.15% 2 sp QD	251	18.5	-3.4	-1.4	-2.1, -0.7	<0.001
	Pbo 2 sp QD	254	18.8	-2.0			
iTNSS	Ap 0.15% 2 sp QD	251	8.9	-1.4	-0.6	-0.9, -0.3	<0.001
	Pbo 2 sp QD	254	8.9	-0.8			

* Sum of AM and PM reflective TNSS (maximum score = 24) averaged over 14 days treatment period, sum of AM and PM instantaneous TNSS for studies 433 and 438, and AM instantaneous TNSS for studies 439, 440, and 443.

† Ap 0.15 % = Astepro 0.15 % Nasal Spray; Ap 0.10 % = Astepro 0.10 % Nasal Spray; As 0.1% = Astelin 0.1% Nasal Spray; Pbo = Placebo Nasal spray;

Table 3. PAR studies, Mean change from baseline in selective efficacy variables*

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from placebo LS mean	95% CI	P value
Study MP 434							
rTNSS	Ap 0.15% 2 sp BID	192	15.8	-4.0	-0.9	-1.7, -0.1	0.03
	Ap 0.10% 2 sp BID	194	15.5	-3.8	-0.7	-1.5, 0.1	0.08
	Pbo 2 sp BID	192	14.7	-3.1			
iTNSS	Ap 0.15% 2 sp BID	192	14.3	-3.4	-0.9	-1.6, 0.1	0.03
	Ap 0.10% 2 sp BID	194	13.9	-3.3	-0.8	-1.6, -0.02	0.05
	Pbo 2 sp BID	192	13.3	-2.5			

* Sum of AM and PM reflective TNSS (maximum score = 24) averaged over 14 days treatment period

† Ap 0.15 % = Astepro 0.15 % Nasal Spray; Ap 0.10 % = Astepro 0.10 % Nasal Spray; As 0.1% = Astelin 0.1% Nasal Spray; Pbo = Placebo Nasal spray;

SAR in patients 12 years of age and older:

Astepro 0.15% at doses of 2 sprays twice daily and 2 sprays once daily is supported by the results of two studies (MP 433, and MP 438) and three studies (MP 439, MP 440, and MP 443), respectively (Table 2). In all of these studies Astepro 0.15% was statistically significantly superior to placebo for the primary efficacy endpoint of rTNSS. Secondary efficacy endpoints were also supportive of efficacy. Particularly, iTNSS, which captures end of dosing interval efficacy, hence the dosing interval, was statistically significantly superior to placebo in one study where Astepro 0.15% was administered twice daily study (MP 438) and two studies where Astepro 0.15% was administered once daily (MP 440, and MP 443). One point to note is that studies MP 440 and MP 443 were conducted in patients with sensitivity to Texas Mountain Cedar. Texas Mountain Cedar is known to provoke intense rhinitis symptoms and often clinical studies conducted in SAR patients allergic to this allergen may show a more robust treatment difference compared to clinical studies conducted in SAR patients allergic to heterogeneous seasonal allergens. Nevertheless, Texas Mountain Cedar is an acceptable model to study SAR. Furthermore, in the clinical program there is adequate replication to support the once daily dosing regimen.

Astepro 0.15% at a dose of 1 spray twice daily was not studied in SAR or PAR patients. However, the 1 spray twice daily dosing is supported based upon the Agency's previous findings of efficacy for Astelin and favorable comparisons of Astepro 0.15% to Astepro 0.1% and to Astelin (Table 2 Study MP 433 and MP 438). Both Astepro 0.1% and Astelin already carry the 1 spray twice daily dosing recommendation.

PAR in patients 12 years of age and older:

Astepro 0.15% at a dose of 2 sprays twice daily is supported by results of one study (MP 434). In this study Astepro 0.15% was statistically significantly superior to placebo for the primary efficacy endpoint of rTNSS. As in the SAR studies, secondary efficacy endpoints, including iTNSS, were statistically significantly superior to placebo (Table 3). A single study to support the PAR indication is acceptable because Astepro 0.15% was shown to have efficacy in SAR.

Astepro 0.15% in addition to Astepro 0.1%:

Approval of Astepro 0.15% in addition to Astepro 0.1%, which is already approved, is supported primarily by two reasons. First, in both SAR and PAR patients, Astepro 0.15% showed a numerically favorable efficacy trend over Astepro 0.1% (MP 438 in Table 2, and MP 434 in Table 3). Therefore, some patients who do not achieve adequate symptom relief from the lower strength may benefit from the higher strength. Second, Astepro 0.15% will have the PAR indication, which Astepro 0.1% does not have. It is known that showing efficacy in PAR is more difficult than SAR. Therefore, it is reasonable for only the higher strength product to carry the PAR indication, pending specific studies with the lower strength product.

8. Safety

a. Safety database

The safety assessment of Astepro 0.15% is based on studies listed in Table 1. The overall safety database was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Astepro 0.15% in patients 12 years of age and older. There were no deaths in the clinical program. Serious adverse events were few and did not suggest a new safety signal. Common adverse events that occurred more in Astepro 0.15% treated patients compared to placebo were bitter taste, nasal discomfort, epistaxis, and sneezing. In the 12-month safety study, reporting of adverse events was similar and did not raise any safety concerns.

Addition of the two sweetening agents did not seem to mask the bitter taste of azelastine. In the 2-4 week studies, bitter taste was the most common adverse event reported, with a frequency of 6% versus 1% with Astepro 0.15% versus placebo, respectively, in 2 sprays twice daily dosing regimen, and 4% versus <1% with Astepro 0.15% versus placebo, in 2 sprays once daily dosing regimen. This is not surprising because bitter taste receptors are in the back of the tongue whereas sweet taste receptors are mostly at the tip of the tongue. A nasal spray formulation drips to the back of the tongue and does not reach the tip of the tongue in any substantial amount.

c. REMS/RiskMAP

There are no substantial safety concerns that would require a REMS or RiskMAP. Other antihistamines also do not have REMS and RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Azelastine is not a new molecular entity. Antihistamines, including nasal antihistamines, are a well studied drug class, and efficacy and safety of this class of drug, including azelastine, is fairly well understood. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

The history of the pediatric study plan is lengthy and part of it predates the Agency's PREA Authority. These are not captured in detail in the primary medical officer review or in the CDTL. Therefore, this review captures the history in some detail.

At the time of first approval of azelastine nasal spray 0.1% for SAR in patients 12 years of age and older at a dose of 2 spray twice daily (Astelin, NDA 20-114, approved on November 1, 1996), no pediatric studies were requested and no pediatric plan was provided. At the time of approval of a supplement to expand the SAR indication to

patients 5 to 11 years of age (Astelin, NDA 20-114, S-005, approved on May 30, 2000), the Division requested that the Applicant submit a pediatric plan or request a waiver for pediatric studies. The Applicant submitted a request for waiver on November 17, 2001, which was denied. The Division then issued a pediatric Written Request on September 20, 2002, which the Applicant declined. At the time of approval of a supplement of the 1 spray twice daily dosing regimen in patients 5 years of age and older (Astelin, NDA 20-114, S-014, approved on February 17, 2006), the issues of pediatric studies were revisited. At that time, PREA had recently gone into effect but the Agency's authority to enforce PREA requirements was under legal challenge. As a result, the approval letter did not explicitly list pediatric studies for SAR as a formal post-marketing commitment. Instead, the following comment was included in the approval letter*: "Although it is not necessary for you to submit detailed pediatric plans for your product at this time, you must still provide a general summary of your pediatric drug development plans. Submit a summary of your pediatric drug development plans to address the requirements of the Pediatric Research Equity Act (PREA), as described in the acknowledgment letter dated June 14, 2005, for NDA 20-114, SE2-014."* In response to this comment, the Applicant stated their plan to conduct a Phase 4 study in SAR in patients 2 to <5 years of age with a related intranasal azelastine product (Astepro 0.1%, a different formulation of azelastine containing two additional excipients, sucralose and sorbitol, added to give the formulation a sweet taste with the intent that the sweet taste will mask the distinctive bitter taste of azelastine) that was in development at the time of the approval of Astelin NDA 20-114, Supplement 014. Studies under the age of 2 years were not planned as SAR is not considered to exist in patients below 2 year of age. The Division was in agreement with this plan.

At the time of approval of azelastine nasal spray 0.1% containing the excipients sucralose and sorbitol for SAR in patients 12 years of age and older at a dose of 2 sprays twice daily (Astepro, NDA 22-203, approved on October 15, 2008), no pediatric studies were required because PREA was not triggered as there was no new active ingredient, no new indication, no new dosage form, no new dosing regimen, or no new route of administration.

This current submission triggers PREA because Astepro 0.15% is proposed for the treatment of PAR, a new indication that neither Astelin nor Astepro 0.1% currently carry. Also, Astepro 0.15% is proposed for a new SAR dosing regimen, 2 sprays once daily. This submission was discussed at the Pediatric Exclusivity Review Committee (PeRC) on April 29, 2009. It was decided that pediatric studies will be required for Astepro 0.15% in PAR for patients 6 months to 11 years of age. The Division noted that for SAR, Astelin was approved in children down to 5 years of age and noted the outstanding agreement for studies in children 2-5 years of age. The Division considers SAR does not exist or difficult to diagnose below 2 years of age, and PAR does not exist or is difficult to diagnose below 6 months of age.

After meeting with PeRC, the Division noted that the outstanding agreement for SAR in children 2 to 5 years of age was not a documented formal post-marketing commitment (PMC). Therefore, the Division will issue a formal post-marketing requirement (PMR)

for SAR studies for patients 2 to 11 years of age and PAR studies in patients 6 months to 11 years of age. Although Astelin is already approved in patients 5 years and older for SAR, no pediatric studies with Astepro have been conducted; therefore, studies as described above will be required. The Applicant was informed of the pediatric requirement and submitted a pediatric program to address the PREA requirements.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was requested for this application because azelastine nasal spray is a well studied product, and the clinical studies conducted with Astepro 0.15% were fairly routine standard studies. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There was one investigator with significant equity interest in MEDA or its predecessor. The number of subjects that this investigator enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC.

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the proprietary name Astepro was reviewed previously with the 0.1% strength product and found to be acceptable.

b. Physician Labeling

The applicant modified the existing Astepro 0.1% to included Astepro 0.15% data in the existing label to have one unified label for the two dosage strengths. Various sections of the label were modified with addition of new data generated with Astepro 0.15% to support the new PAR indication and new dosing regimen for the SAR indication. 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 instructions for use was reviewed by various disciplines of this Division, and DRISK, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Astepro Nasal Spray 0.15% for relief of symptoms of SAR in patients 12 years of age and older at doses of 1 or 2 sprays twice daily or 2 sprays once daily, and in PAR in patients 12 years of age and older at a dose of 2 sprays per nostril twice daily. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk and benefit assessment of Astepro 0.15% supports its approval for relief of symptoms of SAR and PAR in patients 12 years of age and older without any specific restrictions. The submitted clinical program showed efficacy in SAR and PAR patients ages 12 years and older, and the safety profile was acceptable. The safety findings of note were adverse events of bitter taste, nasal discomfort, epistaxis, and sneezing. These are consistent with other antihistamine nasal formulations including Astelin 0.1%.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Pediatric studies as discussed in section 10 above.

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/s/

BADRUL A CHOWDHURY
08/31/2009