CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 20, 2009
From	Sally Seymour, MD, Medical Team Leader, DPAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA# 22-371
Proprietary / Established (USAN) names	Astepro Nasal Spray 0.15% azelastine hydrochloride nasal spray 0.15%
Dosage forms /strength	Nasal spray 0.15%
Proposed Indication(s)	1. Seasonal allergic rhinitis in patients years of age and older 2. Perennial allergic rhinitis in patients 12 years of age and older
Recommended:	Approval

1. Introduction

MEDA submitted a 505(b)(1) new drug application (NDA# 22-371) on August 1, 2008, for a higher strength (0.15%) sweetened azelastine nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older and for the treatment of symptoms of perennial allergic rhinitis (PAR) in patients 12 years of age and older. The PDUFA date for this application is June 1, 2009. An unsweetened azelastine nasal spray is currently approved for the treatment of symptoms of SAR and vasomotor rhinitis (VMR) under the tradename Astelin Nasal Spray (NDA# 20-114), but because of the bitter taste, MEDA developed a sweetened formulation, which contains the excipients, sucralose and sorbitol. The sweetened formulation of azelastine nasal spray 0.1% was approved on October 15, 2008, under the tradename Astepro Nasal Spray (NDA# 22-203) for the treatment of symptoms of SAR in patients 12 years of age and older. In this application for the azelastine nasal spray 0.15%, the proposed dosing regimen is 1-2 sprays twice daily for the SAR indication and 2 sprays twice daily for the PAR indication. Originally, MEDA also proposed a once daily dosing regimen, but following review this dosing regimen was not supported as discussed in Section 7. The proposed tradename is not agreed upon at the time of finalization of this review. The Division prefers Astepro Nasal Spray 0.15% because this is a higher strength formulation of a currently approved product, Astepro Nasal Spray.

Throughout this memo, the drug product for this application will be referred to as azelastine nasal spray 0.15% or azelastine 0.15%. This memo will provide an overview of the application, with a focus on any review issues that warrant discussion: the PAR indication, which is not a current indication for any of the other azelastine nasal sprays; lack of support for the once daily dosing regimen; and labeling issues, including concerns with the tradename. There is a disagreement between the primary Medical Officer and primary statistical reviewer recommendation regarding the once daily dosing regimen that will be addressed in this memo.

2. Background

Azelastine hydrochloride is a selective, H_1 antihistamine, and is approved in the US in an ophthalmic solution, Optivar, and in a nasal spray solution, Astelin Nasal Spray. Astelin Nasal

Spray was originally approved in the US in November 1996 for the treatment of SAR at a dosage of two sprays per nostril twice daily and in February 2006, as one spray per nostril twice daily. Azelastine hydrochloride nasal spray is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide, including most of Europe, 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 twice daily
    - Adults and children 12 years of age and older -1 or 2 sprays per nostril twice daily
- Vasomotor rhinitis (VMR) in adults and children 12 years of age and older - 2 sprays per nostril twice daily

Astepro Nasal Spray 0.1% (NDA# 22-203) is a sweetened formulation of azelastine nasal spray which contains the excipients, sucralose and sorbitol. The sweetened formulation of azelastine nasal spray 0.1% was approved on October 15, 2008, for the treatment of symptoms of SAR in patients 12 years of age and older. Clinical studies were required for this change in formulation because of the novel excipients. MEDA did not conduct clinical trials in patients with VMR or in children with SAR < 12 years of age; therefore, the indication for Astepro is for patients with SAR 12 years of age and older. The approved dose is 1 or 2 sprays per nostril twice daily.

MEDA developed the 0.15% formulation to demonstrate improved efficacy over Astelin Nasal Spray and support once daily administration. In terms of regulatory history regarding the higher strength formulation (0.15%), there have been limited interactions between MEDA and the Division regarding this development program. On August 29, 2006, a meeting was held between the Division and MEDA. The following issues with the program were identified: a VMR indication would need clinical studies; unclear rationale for the two different strength (0.1% and 0.15%) products; the proposed study would not be adequate to support once daily dosing because the placebo used in the afternoon may confound the efficacy findings.

3. CMC/Device

Azelastine nasal spray 0.15% is a new higher strength formulation of azelastine hydrochloride nasal spray that contains sucralose and sorbitol. The product is an aqueous solution with a pH of 6.4 that contains 0.15% (1.5mg/mL) azelastine hydrochloride, which is the same active drug substance, in Astelin Nasal Spray and Astepro Nasal Spray. The drug substance is manufactured by MEDA Pharma GmbH & Co. KG, (formerly Viatris GmbH) in Germany. Azelastine nasal spray 0.15% delivers 205.5 mcg azelastine hydrochloride (or 187 mcg azelastine base) per 0.137mL actuation. The excipients are the same as Astepro Nasal Spray, with the exception that the (b) (4) (b) (4) The drug product is packaged as (b) (4) in a 34.5mL high density polyethylene bottle fitted with a metered spray pump. There is also a physician sample product which is packaged in a 15mL bottle with a fill volume of (b) (4). The (b) (4) fill volumes are sufficient to provide 200, 106, and 22 sprays per bottle. The drug product is manufactured by MEDA Pharmaceuticals in Decatur, Illinois.

The CMC reviewer noted that there are no changes in the drug substance (including specifications) for this NDA. The manufacturing and testing facilities for the drug substance and product are the same as for the other azelastine nasal spray product. The submitted data support that azelastine nasal spray 0.15% (17 and 30mL fill packages) can be stored at room temperature with an expiry of 24 months.

The cGMP inspection status of all manufacturing and testing facilities was found acceptable as of March 18, 2009. The EER status is acceptable. There are no outstanding CMC issues and the CMC reviewer, Dr. Martin Haber, recommends Approval.

4. Nonclinical Pharmacology/Toxicology

A full toxicology battery was submitted and previously reviewed under NDA 20-114 for Astelin Nasal Spray. Additional toxicology studies were submitted and previously reviewed under NDA# 22-203 for Astepro Nasal Spray. To support azelastine nasal spray 0.15%, MEDA submitted a bridging toxicology program comparing Astelin Nasal Spray, Astepro Nasal Spray, and azelastine nasal spray 0.15%. The bridging program consisted of an intranasal 6 month toxicity study in rats with Astelin Nasal Spray, Astepro Nasal Spray (0.1%), and azelastine nasal spray 0.15%. According to the pharmacology/toxicology reviewer, Dr. Luqi Pei, the results showed that the 3 products had similar toxicity profiles, i.e. local irritation of the nasal cavity. Dr. Pei recommends Approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data was submitted in this application. One relative bioavailability (BA) study (Study MP429) and one multiple dose pharmacokinetics (PK) study (Study 25) have been re-submitted by the sponsor. These studies have been reviewed under NDA 22-203 and NDA 22-114 previously. The results of the relative BA study indicate that the pharmacokinetics parameters, CL, $T_{1/2}$, and T_{max} for azelastine and its major active metabolite, desmethylazelastine are comparable among the three treatments: commercial formulation of 0.1% Astelin (total dose: 548 mcg), approved formulation of Astepro 0.1% (total dose: 548 mcg), and the proposed higher strength formulation of azelastine nasal spray 0.15% (total dose: 822 mcg). In addition, in the multiple dose PK study, azelastine hydrochloride did not demonstrate either dose proportionality or time-independent PK due to the large variability of the data leading to inconsistent results in these analyses.

Dr. Ying Fan was the clinical pharmacology reviewer for this application. Dr. Fan finds this application acceptable provided agreed upon labeling.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical- Efficacy

The Applicant submitted seven clinical studies to support this application: one proof of concept study in patients with PAR; four efficacy and safety studies in patients with SAR; 2 efficacy and safety studies in patients with PAR; and one long term safety study in patients

with PAR. The studies are outlined in the table below. The primary focus of this section is the efficacy studies in SAR and PAR patients. The ongoing one year safety study (Study MP436) will be described in this section, but the results will be presented in Section 8, Safety. In addition, the 12 month results of the recently completed one year safety study with Astepro 0.1% (Study MP432) became available during the review and will be addressed in Section 8. A detailed review of the clinical studies can be found in Dr. Susan Limb's clinical review with detailed statistical analyses in Ted Guo's statistical review.

Table 1 Clinical Development Program for Azelastine Nasal Spray 0.15%

Study	Design	Duration	Population	Treatment Groups (n)†
MP435 Jan 2007 – May 2007 US	MC, R, DB, PC **Proof of concept - PAR**	4 weeks	156 patients PAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril QAM (n=53) azelastine 0.15% - 2 sprays per nostril QPM (n=52) placebo vehicle – 2 sprays per nostril QAM (n=24) placebo vehicle – 2 sprays per nostril QPM (n=27)
MP433 Aug 2006-Nov 2006 US	MC, R, DB, PC, AC **Efficacy and safety - SAR**	2 weeks	617 patients SAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril BID (n=153) azelastine 0.15% - 2 sprays per nostril QAM and 2 sprays per nostril placebo vehicle QPM (n=158) Astelin - 2 sprays per nostril BID (n=153) placebo vehicle – 2 sprays per nostril BID (n=153)
MP438 Aug 2007 – Nov 2007 US	MC, R, DB, PC, AC **Efficacy and safety - SAR**	2 weeks	526 patients SAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril BID (n=178) Astepro 0.1% - 2 sprays per nostril BID (n=170) placebo vehicle – 2 sprays per nostril BID (n=178)
MP439 Aug 2007-Nov 2007 US	MC, R, DB, PC **Efficacy and safety - SAR**	2 weeks	467 patients SAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril QD (n=239) placebo vehicle – 2 sprays per nostril QD (n=242)
MP440 Dec 2007 – Feb 2008 US	MC, R, DB, PC **Efficacy and safety - SAR** Texas Mountain Cedar	2 weeks	536 patients SAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril QD (n=268) placebo vehicle – 2 sprays per nostril QD (n=268)
MP434 Feb 2007-Oct 2007 US	MC, R, DB, PC, AC **Efficacy and safety - PAR**	4 weeks	581 patients PAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril BID (n=192) Astepro 0.1% - 2 sprays per nostril BID (n=197) placebo vehicle – 2 sprays per nostril BID (n=192)
MP436 Jan 2007-Jan 2008 US	MC, R, OL, AC **Long term safety - PAR** **ongoing**	12 months	703 patients PAR 12 yrs and older	azelastine 0.15% - 2 sprays per nostril BID (n=465) Nasonex – 2 sprays per nostril BID (n=238)

† randomized

The pivotal efficacy studies listed in the table above had many similarities in design and conduct. Therefore, the studies and results are discussed in an integrated fashion below based upon the proposed indication. Pertinent differences in study design will be highlighted. The general design and inclusion/exclusion criteria of these studies are consistent with the Draft Guidance for Industry: Allergic Rhinitis- Clinical Development Programs for Drug Products.

Seasonal Allergic Rhinitis – Study Design

Studies MP433, MP438, MP439, and MP440 were multicenter, randomized, double-blind, placebo controlled clinical trials of 2 weeks duration in patients 12 years of age and older with seasonal allergic rhinitis. Eligible patients had a minimum 2 year history of SAR with a

positive skin test to a relevant fall allergen. For study MP440, the allergen was specified as Texas Mountain Cedar. Following a one week, single-blind, placebo run in period, patients were randomized to specified treatment groups shown in the table above. The following are important features of the individual studies:

- Study MP433 included an azelastine 0.15% QAM and placebo QPM treatment group to assess once daily dosing of azelastine 0.15%. However the inclusion of the placebo in the afternoon may confound the efficacy findings. This design issue was conveyed to MEDA in the August 2006 meeting.
- Studies MP439 and MP440 were designed to assess the efficacy of once daily dosing
- Study MP433 and MP438 included an active control of Astelin and Astepro, respectively

Efficacy in all the studies was assessed by the Total Nasal Symptom Score (TNSS), which included the following symptoms: runny nose, sneezing, itchy nose, and nasal congestion. Patients recorded scores for these symptoms on a 0 to 3 (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms) scale twice daily, in the morning (AM) and evening (PM) in patient diaries. Patients recorded both a 12 hour reflective score (how symptoms were over the previous 12 hours) and an instantaneous score (how symptoms are at the time of evaluation). For the primary efficacy endpoint, the AM and PM reflective TNSS (rTNSS) were summed for each day (maximum score of 24) and then averaged over the 14 day treatment period.

Secondary efficacy variables included onset of action over the 4-hour period following the initial dose of study medication, instantaneous TNSS (iTNSS), individual symptom rTNSS scores, and the change from baseline to Day 14 in Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is a validated instrument for assessing the impact of rhinitis on activities of daily living and overall well-being. It is a 28-item, disease-specific instrument designed to measure the seven domains of functional impairment that are most important to patients with SAR: sleep impairment, non-nasal symptoms (e.g., headache and fatigue), practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function. There is also an overall quality of life score for the RQLQ that is expressed as the mean of the seven individual domains. Patients are asked to consider their experiences over the previous seven days and to score their degree of impairment on a seven-point scale (0 = not bothered, 6 = extremely bothered).

Efficacy analyses were performed on the intent to treat population, defined as all randomized patients who had at least one post-baseline assessment. Baseline was defined as the average of all TNSS scores over the 7 day placebo run-in period. Onset of action was defined as the first timepoint after initiation of treatment when the active drug demonstrated a change greater than placebo from baseline in the iTNSS and was maintained. The iTNSS was measured frequently during the first 4 hours after study medication administration on day one.

Perennial Allergic Rhinitis – Study Design

Study MP434 was similar in design to the SAR studies except that eligible patients had a minimum 2 year history of PAR with IgE mediated hypersensitivity to dust mite, cockroach, mold, cat, or dog dander. In addition, the study was 4 weeks duration. Primary and

secondary efficacy variables were similar to the SAR studies. If the SAR indication is supported, only one PAR study is necessary for the PAR indication (Draft Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products).

Long-term Safety Study

Study MP436 is a multicenter, randomized, open-label, active controlled 12 month clinical trial conducted to evaluate the long term safety of azelastine nasal spray 0.15% in patients 12 years of age and older with PAR. Eligible patients had a history of PAR with IgE mediated hypersensitivity to dust mite, cockroach, mold, cat, or dog dander and were randomized 2:1 to azelastine 0.15% 2 sprays BID or Nasonex 2 sprays QD. Efficacy was assessed by the RQLQ. Compliance was assessed by recording of doses in a diary and bottle weights.

Efficacy Results

The results for the primary endpoint as determined by the Division's statistical reviewer, Dr. Ted Guo are shown in the table below. The numbers differ slightly from the Applicant's numbers, which are the result of differences in the model used for analysis.

Table 2 Efficacy Results
LS Mean Change from Baseline in Reflective TNSS *

Treatment	n†	Baseline LS Mean	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
Seasonal Allergic Rhinitis						
Study MP433 – SAR (2 weeks)						
Azelastine 0.15% - 2 sprays per nostril BID	153	18.2	-4.3	-1.2	-2.1, -0.3	0.01
Azelastine 0.15% - 2 sprays per nostril QAM and placebo 2 sprays per nostril QPM	158	18.6	-3.9	-0.8	-1.7, 0.1	0.08
Astelin – 2 sprays per nostril BID	153	17.9	-3.9	-0.9	-1.8, 0.1	0.07
Placebo – 2 sprays per nostril BID	153	18.1	-3.0			
Study MP438 – SAR (2 weeks)						
Azelastine 0.15% - 2 sprays per nostril BID	177	17.7	-5.1	-3.0	-3.9, -2.1	<0.001
Astepro 0.1% – 2 sprays per nostril BID	169	18.1	-4.2	-2.1	-3.0, -1.2	<0.001
Placebo – 2 sprays per nostril BID	177	17.7	-2.1			
Study MP439 – SAR (2 weeks)						
Azelastine 0.15% - 2 sprays per nostril QD	238	17.4	-3.4	-1.0	-1.7, -0.3	0.008
Placebo – 2 sprays per nostril QD	242	17.4	-2.4			
Study MP440 – SAR (2 weeks) – Texas Mountain Cedar						
Azelastine 0.15% - 2 sprays per nostril QD	266	18.5	-3.3	-1.4	-2.1, -0.8	<0.001
Placebo – 2 sprays per nostril QD	266	18.0	-1.9			
Perennial Allergic Rhinitis						
Study MP434 – PAR (4 weeks)						
Azelastine 0.15% - 2 sprays per nostril BID	192	15.8	-4.0	-0.9	-1.7, -0.07	0.04
Astepro 0.1% – 2 sprays per nostril BID	194	15.5	-3.8	-0.7	-1.5, 0.09	0.08
Placebo – 2 sprays per nostril BID	192	14.7	-3.1			

*sum of AM and PM rTNSS for each day and averaged over a 14 day treatment period; 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion; max score 24
† - ITT

Seasonal Allergic Rhinitis – 1-2 sprays BID

In the SAR studies, azelastine 0.15% two sprays BID was statistically significant compared to placebo in Studies MP433 and MP438. The inclusion of the active comparators, Astelin and

Astepro, in Studies MP433 and MP438 provide information regarding the higher strength product compared to the currently marketed 0.1% products. In both studies, azelastine 0.15% provided a greater numerical treatment effect compared to Astelin and Astepro. This suggests that some patients may benefit more from the azelastine 0.15%product, which provides justification for the higher strength formulation. The results for the secondary endpoints were generally consistent with the primary endpoint.

Astelin Nasal Spray and Astepro Nasal Spray are currently approved for 1-2 sprays BID. The clinical program for azelastine 0.15% did not include data for the one spray BID treatment regimen. However, based upon the finding that one spray of Astelin or Astepro are effective for SAR and azelastine 0.15% has a numerical treatment benefit compared to these products, it is reasonable to conclude that one spray of azelastine 0.15% will also be effective. Dosing of 1-2 sprays BID would be consistent with the other azelastine nasal sprays and would allow for titration of the higher strength product.

Seasonal Allergic Rhinitis – 2 sprays QD

Astelin Nasal Spray and Astepro Nasal Spray are currently approved for twice daily administration. The results of Studies MP439 and MP440 show that azelastine 0.15% QD was statistically significant compared to placebo. However, assessment of instantaneous symptoms scores at the end of dosing interval is necessary to evaluate the duration of treatment effect. According to the Draft Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products, a sponsor should demonstrate a significant difference between drug and placebo at the end of the dosing interval. Since the QD dosing regimen is new for an azelastine nasal spray, a close look at the AM iTNSS scores is warranted. The results for Study MP439 and MP440 are shown below.

Table 3 Efficacy Results
LS Mean Change from Baseline in AM Instantaneous TNSS *

Treatment	n	Baseline LS Mean	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
Seasonal Allergic Rhinitis						
Study MP439 – SAR (2 weeks)						
Azelastine 0.15% - 2 sprays per nostril QD	238	8.1	-1.3	-0.3	-0.64, 0.10	0.147
Placebo – 2 sprays per nostril QD	242	8.3	-1.1			
Study MP440 – SAR (2 weeks) – Texas Mountain Cedar						
Azelastine 0.15% - 2 sprays per nostril QD	266	8.7	-1.4	-0.7	-1.04, -0.37	<0.001
Placebo – 2 sprays per nostril QD	266	8.3	-0.7			

*MEDA analysis, ITT population ; Vol 40, Table 14.2.7.1, Vol 55, Table 14.2.7.1

The results of the AM iTNSS for the once daily dosing of azelastine 0.15% do not show a consistent statistically significant difference compared to placebo. In Study MP440, the results were statistically significant compared to placebo, but not in Study MP439. Thus, there is not replication of the AM iTNSS to support this new proposed once daily dosing interval. This is the conclusion and recommendation of the medical reviewer, Dr. Limb. In addition, as noted by Dr. Limb, Study MP440 was conducted in patients with allergy to Texas mountain cedar, which can provoke intense rhinitis symptoms. Clinical trials conducted in this SAR population may demonstrate robust treatment differences, which may explain why Study

MP440 was significant for the AM iTNSS. The primary statistical reviewer, Dr. Guo, recommended approval of the once daily dosing interval primarily based upon the results of the primary endpoint, combined AM and PM rTNSS. Because the AM iTNSS does not consistently support the once daily dosing regimen, which is a new dosing regimen for azelastine, this reviewer concurs with Dr. Limb. There is no replication of the AM iTNSS to support the once daily dosing regimen.

Perennial Allergic Rhinitis – 2 sprays BID

In this application, MEDA proposes a PAR indication for azelastine 0.15% nasal spray. One study, Study MP434, was submitted to support the new indication. The results from Table 2 show that azelastine 0.15% was statistically significant compared to placebo. The results for the secondary endpoints were generally consistent with the primary endpoint. This information combined with the efficacy results from the SAR studies is adequate to support the proposed PAR indication.

RQLQ

MEDA did not propose a labeling claim for the RQLQ; and, the data submitted in this application are not adequate to support a RQLQ claim. To support an RQLQ claim for azelastine 0.15%, the treatment difference for the RQLQ would need to be statistically significant compared to placebo, cross the minimum clinically important difference threshold of 0.5, and replicated. The results show that in Study MP433, the RQLQ was numerically improved on Day 14 for the azelastine 0.15% 2 sprays BID treatment group compared to placebo, but the difference (0.31) did not meet the MID and was not statistically significant ($p=0.07$). In Study MP438, the RQLQ on Day 14 for the azelastine 0.15% 2 sprays BID treatment group was statistically significant ($p<0.001$) compared to placebo, and the difference in the change from baseline RQLQ between azelastine 0.15% and placebo (-0.52) met the MID.

Onset of Action

MEDA does not seek an onset of action claim in this NDA. Astelin Nasal Spray currently has an onset of action labeling claim of within 3 hours. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference between the active and placebo is statistically significant and the difference persists consistently after that time point. In Study MP433, onset of action was not established for the 0.15% azelastine group as the iTNSS was not consistently significant compared to placebo in the first 4 hours following the first dose. In Study MP438, the onset of action for the azelastine 0.15% group was 30 minutes. However, since the finding is not replicated, an onset of action claim is not supported.

Dr. Susan Limb concludes that the submitted data is sufficient to support the SAR and PAR indication for azelastine 0.15% 1-2 sprays in patients 12 years of age and older. However, she has concluded that the once daily dosing regimen is not supported. I concur with these conclusions. Her recommendation is for Approval.

8. Safety

The safety of azelastine 0.15% is based upon the clinical trials outlined in Table 1 as well as the known safety profiles of Astelin Nasal Spray and Astepro Nasal Spray. A total of 996 patients received azelastine 0.15% in studies of 2 weeks to 4 weeks duration. In addition, a total of 465 patients received azelastine 0.15% in the ongoing 12 month safety study. Safety evaluations in the clinical program included adverse events, vital signs, and physical examinations (focused examination of the head and neck). The design, patient population, and drug exposure in this program were adequate to assess the safety of azelastine 0.15% in patients 12 years of age and older.

There were no deaths in the clinical program. SAEs were few and did not suggest a new safety signal. The discontinuations due to adverse events also did not suggest a new safety signal as the types of events were similar to events reported during the trials.

The adverse event results showed that dysgeusia, epistaxis, headache, nasal discomfort, and upper respiratory tract infection are associated with the use of azelastine 0.15%. These results are consistent with the known safety profile of Astelin Nasal Spray and Astepro Nasal Spray. No clinical laboratories other than screening were performed in these trials. The vital sign and physical examination data did not suggest a new safety signal. The long term safety data did not identify a new safety signal.

Because local nasal toxicity is a known effect of azelastine nasal spray, Dr. Limb reviewed these adverse events carefully. She noted that the common local toxicity adverse events, such as nasal discomfort, epistaxis, pharyngolaryngeal pain, and nasopharyngitis, were similar among the treatment groups. In addition, there was no dose related effect with azelastine nasal spray. No new cases of nasal ulceration or septal perforation were noted. In study MP434, one patient in the azelastine 0.1% group was reported as having a nasal septum perforation, which the investigators deemed unlikely to be related to treatment because the patient reported that the perforation had been present since 1997, well before the study. Although the perforation was not reported on screening form, with the history of a perforation and short duration of exposure, no causality to azelastine can be definitively attributed.

Similarly, because sedation is a known effect of azelastine nasal spray, Dr. Limb reviewed these adverse events carefully. Sedation, somnolence, and fatigue were noted with azelastine 0.15%. This is consistent with Astelin and Astepro Nasal Spray and the labels contain a sedation warning. This language should be included in the labeling for azelastine 0.15%. With regards to sedation, there was no consistent dose related effect.

During the review of this application, the final study report for MP432 was submitted. MP432 was a randomized, active-controlled, open-label, 12 month clinical trial to assess the safety of Astepro 0.1% vs. Astelin in patients 12 years of age and older with chronic allergic or non-allergic rhinitis. Six month data from this trial provided long term safety data to support the approval of Astepro 0.1%. A total of 862 patients were randomized – 430 to Astepro 0.1% and 432 to Astelin. Patients were assessed every 3 months and safety evaluations in the clinical program included adverse events, vital signs, and focused examination of the head and neck. Results did not identify a new safety signal. No deaths were reported. SAEs were few

and of a variety of events such that a causal relationship was unlikely. No nasal septal perforations were reported. AEs were similar to the known safety profile of Astelin and the 6 month safety profile of Astepro. Common AEs included headache, nasopharyngitis, epistaxis, and dysgeusia. Interestingly dysgeusia was similar between Astepro (6.5%) and Astelin (7.4%), which suggests the taste-masking agents do not eliminate this complaint. Although this study does not include the azelastine 0.15% formulation, there will be one label for the sweetened azelastine nasal spray formulations and the label will need to include the 12 month safety data for Astepro.

Dr. Susan Limb concluded that the safety profile of azelastine 0.15% is similar to Astelin Nasal Spray and Astepro Nasal Spray. No new safety signals were identified in this clinical program and I concur.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this NDA. Azelastine is currently approved as Astelin Nasal Spray and Astepro Nasal Spray. This Application is for a new strength of azelastine nasal spray (0.15%). Since azelastine is a known drug substance with established safety profile, there are no specific issues that warrant discussion at an Advisory Committee Meeting.

10. Pediatrics

This application triggers PREA because there is a new indication (PAR) for azelastine and there is a new dosing regimen.

In the original Astelin NDA (NDA# 20-114) approved in November 1996, the indication was for patients with SAR 12 years of age and older. On May 30, 2000, Astelin was approved for SAR in children 5 years of age and older and in the approval letter, pediatric studies in children 2 to 5 years of age were requested. In the AP letter, the applicant was asked to submit a pediatric development plan. A Written Request was issued on September 20, 2002, for studies in children 2 to < 5 years of age. The Written Request was for a safety and PK study in children 2 to 5 years of age with allergic rhinitis. In 2004, the Sponsor advised the Division that they did not plan to conduct the study outlined in the Written Request. With the February 17, 2006, approval of the 1 spray dose in patients 12 years of age and older for SAR, studies in children less than 2 years of age were waived and studies in children 2 to 5 years of age were deferred. Studies in children < 2 years of age were waived primarily because the diagnosis of SAR in this age group is questionable. The sweetened formulation of azelastine nasal spray (Astepro NDA# 22-203) did not trigger PREA. At this time, the pediatric studies in children 2 to 5 years of age with SAR have not been conducted. MEDA indicated plans to use the sweetened formulation (Astepro) for the pediatric studies in children 2 to 5 years of age.

In this application, the Applicant requested a complete waiver of pediatric studies in children < 12 years of age for azelastine 0.15%. The rationale for their waiver is that Astelin Nasal Spray is approved for SAR in patients 5 to 11 years of age (1 spray per nostril twice daily) and MEDA does not believe a higher exposure (0.15%) is justified in children.

Regarding SAR, studies in children down to 5 years of age have been completed with azelastine nasal spray (Astelin). Additional studies in this age group with azelastine 0.15% are not necessary. Studies in children 2 to 5 years of age with SAR will be deferred as MEDA already has an outstanding commitment in this age group with Astelin. Regarding PAR, although there are other antihistamine formulations to treat PAR in patients less than 12 years of age, MEDA should evaluate the safety and efficacy azelastine in children < 12 years of age with PAR. Part of the pediatric program should entail determining the appropriate dose in children for PAR, which may be the Astepro 0.1% formulation. Thus, the recommendation is for a deferral of pediatric studies in children 6 months to < 12 years of age with PAR. A waiver in children < 6 months of age is reasonable given the fact that the diagnosis of PAR in this age group is uncertain. The pediatric assessment could potentially support an indication for PAR in patients 6 months of age and older.

This application will be discussed at the Pediatric Review Committee (PERC) on April 29, 2009.

11. Other Relevant Regulatory Issues

A DSI audit was not requested because Astelin Nasal Spray is an approved drug product with extensive post-marketing experience. This application is for a similar product, but with a higher concentration of azelastine. Because the safety and efficacy of azelastine are well-established and review of the application did not raise any data integrity issues, a DSI audit was not necessary.

12. Labeling

MEDA originally proposed the proprietary name of (b) (4). The Division of Medication Error Prevention (DMEP) reviewed the name and found it unacceptable because of concerns with confusing the different azelastine nasal products. In addition, in the filing letter, the Division raised the concern about use of separate tradenames and separate labels without clear dosing guidelines. A teleconference was held with DMEPA, the Division and MEDA on January 5, 2009. During the teleconference, the Division raised this concern again and clarified our preference to have one label for the azelastine nasal sprays with taste masking agents. MEDA submitted a revised label that incorporated the Astepro information and submitted a new tradename of (b) (4) for the higher strength formulation. DMEPA's determination of the (b) (4) tradename is pending at the time of finalization of this memo. However, the Division's preference would be to have both products with the tradename Astepro Nasal Spray with the 0.1% and 0.15% distinguishing the different strengths of the products. At the time of finalization of this memo, an agreed upon tradename is pending.

The major issues with the label included the following:

- The once daily indication was not supported and removed.
- The label should be organized by indication with the lower strength information before the higher strength.
- Integrating the information for the two different strengths throughout the label in a logical manner.

The Division of Drug Marketing, Advertising and Communication (DDMAC) were consulted to provide comments on the package insert and carton and container labels. The consultation is pending at the time of finalization of this memo.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The submitted data are adequate to support the approval of azelastine nasal spray 0.15% for the relief of the symptoms of SAR and PAR in patients 12 years of age and older. However, the data are not adequate to support the once daily dosing regimen. If MEDA agrees to remove the once daily dosing regimen, the recommendation for this application is Approval.

- Risk Benefit Assessment

The submitted data supports the efficacy of azelastine nasal spray 0.15% in patients with SAR or PAR. The PAR indication is unique to a nasal antihistamine and provides patients with an additional therapeutic option. The submitted data suggested a benefit of the azelastine nasal spray 0.15% over the currently approved azelastine nasal products. The safety profile of azelastine 0.15% is similar to the approved azelastine nasal sprays (Astelin Nasal Spray and Astepro Nasal Spray). There were no consistent dose related effects and no unique safety signals. Thus, the submitted data supports a favorable risk benefit profile in patients with SAR or PAR 12 years of age and older.

- Recommendation for Postmarketing Risk Management Activities

There are no recommendations for post-marketing risk management activities.

- Recommendation for other Postmarketing Study Commitments

There is a recommendation for post-marketing requirements to conduct pediatric studies under PREA in children 6 months to < 12 years of age for the treatment of perennial allergic rhinitis. See Section 10.

- Recommended Comments to Applicant

There are no comments to be conveyed to MEDA.

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/s/

Sally Seymour
4/20/2009 11:27:06 AM
MEDICAL OFFICER