

b(4)

8. Safety

The clinical development program is based upon the comparability of the MP03-33 and Astelin Nasal Spray. However, because of the excipients sucralose and sorbitol, long term safety data was required for this application. The safety of MP03-33 is based upon the results of the 2-week comparability/safety and efficacy study (Study MP430) as well as the interim results from an ongoing 6 month safety study (Study PM432). Because the clinical studies were conducted in patients 12 years of age and older, the safety database is adequate to evaluate safety in this age group. However, _____

_____, therefore, _____
_____ the indication in children 5 to 12 years of age is not supported. The following is a brief summary of the findings in Study MP430 and a description of the design, conduct, and results from Study MP432.

In Study MP430, no new safety signals were identified for MP03-33 compared to the safety profile of Astelin Nasal Spray. There were no deaths or serious adverse events. Eight patients discontinued due to adverse events (5 in the active groups and 3 in the placebo groups). The reasons for discontinuation in the active treatment groups were: rhinitis, dizziness, URTI, allergic conjunctivitis, and heart palpitations. Rhinitis, URTI and allergic conjunctivitis are not unexpected in a clinical trial in allergic rhinitis patients. Dizziness and heart palpitations

are not know adverse reactions with azelastine and since reported in only one patient each, it is difficult to conclude that this is a new safety signal.

The adverse event results showed that dysgeusia, epistaxis, headache, nasal discomfort, fatigue, and somnolence are associated with the use of both Astelin Nasal Spray and MP03-33. These results are consistent with the known safety profile of Astelin Nasal Spray. Astelin Nasal Spray contains a sedation warning in the product label and this language should be included in the labeling for MP03-33. It is interesting to note that the Applicant reformulated because of dysgeusia with the current Astelin Nasal Spray; however, patients continue to report dysgeusia with MP03-33. Of note, nasal ulceration was reported as an adverse event in 3 patients in the Astelin Nasal Spray treatment groups (one in 1 spray and two in 2 sprays) and no patient in the other treatment groups. 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.

Study MP432

Study MP432 is an ongoing, one year, randomized, open-label, active controlled trial of the safety and tolerability of MP03-33 in 860 patients with chronic allergic or nonallergic rhinitis 12 years of age and older. Astelin Nasal Spray was used as the active control in this clinical trial. The inclusion criteria specified that patients must have an established history (>1 year) of rhinitis due to perennial allergies, non-allergic triggers or vasomotor rhinitis. Patients with SAR were included as long as they had significant symptoms outside the allergy seasons. The diagnosis of rhinitis must have been made on the basis of a thorough evaluation, including history, physical examination, symptoms, skin testing or RAST, +/- nasal smears.

Following a one week screening period, patients were randomized to either Astelin Nasal Spray 2 sprays per nostril twice daily or MP03-33 2 sprays per nostril twice daily. Clinic visits were made at Months 1, 3, and 6, and telephone contact at Months 2, 4, and 5. Safety was assessed by adverse events and focused head and neck examinations. The focused examinations rated findings (mucosal edema, nasal discharge, mucosal bleeding, mucosal ulceration, mucosa crusting) on a scale of 0 to 3 (none to severe). The WHO Toxicity Criteria were used to grade nasopharynx adverse events. Patients who developed Grade 3 ulcerations or nasal septal perforations were referred to an otorhinolaryngologist for evaluation. Efficacy was assessed via the Mini RQLQ at all treatment visits in patients 18 years of age and older. The Mini-RQLQ differs from the RQLQ in that it only has 14-items in 5 domains rated on the same 7 point scale as the RQLQ.

The Applicant submitted results from a 6 month interim analysis in 559 patients of which 442 completed 6 months of treatment. The safety population (555 patients) is defined as all randomized patients who received at least one dose of study medication. There were no deaths. The percentage of patients who discontinued due to AEs (6.4%, 5%), reported AEs (50%, 48%), and serious adverse events (0.4%, 1.1%) was similar in the MP03-33 and Astelin Nasal Spray treatment groups, respectively. The most common AEs were headache, dysgeusia, epistaxis, nasopharyngitis, viral infection, and pharyngolaryngeal pain and the frequency was generally comparable between treatment groups. Nasal septal ulceration was reported in one patient in the Astelin Nasal Spray group and no patients in the MP03-33 group.

Somnolence was reported in 1.4%-1.8% of patients in each treatment group providing further support to include the somnolence warning included in the labeling for MP03-33.

On focused nasal examination, no patient had Grade 4 epistaxis (ER visit/hospitalization), ulceration or pain. One patient in the MP03-33 group had Grade 3 epistaxis (significant, prevents daily activity). Although only one patient reported nasal ulceration as an AE, focused nasal examination noted Grade 3 ulcerations in 3.9-3.6% of patients in the MP03-33 treatment group and Astelin Nasal Spray, respectively over the course of the 6 month treatment period compared to Day 1 where Grade 3 ulcerations were noted in 1.8-1.4% of patients in the MP03-33 treatment group and Astelin Nasal Spray, respectively. There were no reports of nasal septal perforation.

The interim results of this ongoing safety study demonstrate that the safety profile of MP03-33 and Astelin Nasal Spray are similar. The adverse events known to be associated with Astelin Nasal Spray (dysgeusia, epistaxis, somnolence, headaches) were also noted with MP03-33. No new safety signals were identified.

The AERS safety database was searched for reports of nasal septal perforations with Astelin Nasal Spray. Two cases were identified. One case was reported in a 32 year old female who was treated with fluticasone nasal spray and Astelin Nasal Spray for the treatment of allergic rhinitis. She was diagnosed with a nasal septal perforation. Fluticasone was discontinued and azelastine was continued. The second case was reported in a 60 year old patient who had a past medical history of two septal reconstructions and was prescribed Astelin for the treatment of VMR and developed a perforated septum. Both cases have confounding factors.

Dr. Susan Limb concluded that the safety profile of MP03-33 is similar to Astelin 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 for adults and adolescents 5 years of age and older. This Application is for a new formulation of azelastine nasal spray that contains sucralose and sorbitol to mask the bitter taste of azelastine. Since the safety and efficacy of Astelin Nasal Spray have already been established, there are no specific issues that warrant discussion at an Advisory Committee Meeting.

10. Pediatrics

This reviewer's understanding is that this NDA does not trigger PREA because there is no new active ingredient (azelastine), no new indication (SAR), no new dosage form (nasal spray), no new dosing regimen (twice a day), or no new route of administration (nasal). Under the Astelin NDA (NDA# 20-114), following the February 17, 2006, approval of the 1 spray dose in patients 5 years of age and older, 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. In addition, the nasal spray formulation may not be appropriate as there are oral antihistamines available in this age group.

b(4)

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 taste-masking agent, sucralose and sorbitol. 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.

The Applicant submitted a request for formal dispute resolution on April 21, 2008. The appeal concerned approval of the VMR indication in adults and the SAR indication in pediatric patients 5 to 12 years of age. However, the request did not qualify as a formal dispute resolution because a decision on the approvability of the proposed indications was still pending.

12. Labeling

The Applicant proposed the proprietary name of [redacted]. The Division of Medication Error Prevention (DMEP) reviewed the name and found it unacceptable because of concerns with confusing the two Astelin products that have different indications. After discussions with the Applicant, they submitted the following additional tradenames: Astepro, [redacted], and [redacted]. At the time of finalization of this memo, an agreed upon tradename is pending.

b(4)

The Applicant submitted the product label in the new physicians labeling rule format (PLR). Much of the information in the proposed product label is appropriately carried forward from the approved Astelin Nasal Spray label. The following is a list of major issues regarding the labeling submitted by the Applicant:

b(4)

The Division of Drug Marketing, Advertising and Communication (DDMAC) provided comments on the package insert and carton and container labels which were reviewed and addressed. The Division of Risk Management provided comments on the patient package insert and patient's instructions for use. These comments were conveyed to the Applicant.

During labeling negotiations, the Applicant did not agree with the Division's determination that the VMR, pediatric, _____ claims are not supported. The Applicant submitted a request for formal dispute resolution on April 21, 2008. However, the request did not qualify as a formal dispute resolution because a decision on the approvability of the proposed indications was still pending. Although the remainder of the labeling was agreed upon, the Applicant clearly stated that they do not agree with the decision regarding the VMR, pediatric, and _____ claim.

b(4)

b(4)

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The submitted data are adequate to support the approval of MP03-33 for the relief of the symptoms of SAR in patients 12 years of age and older. However, the data are not adequate to support the VMR indication and the SAR indication in children 5 to <12 years of age. The recommendation for this application is Not Approvable.

- Risk Benefit Assessment

b(4)

Without clinical data for these populations, a risk benefit analysis cannot be performed. However, as discussed in Section 7 and 8, the submitted data support the efficacy and safety of MP03-33 in patients with SAR 12 years of age and older and generally supports a favorable risk benefit profile in this population.

- Recommendation for Postmarketing Risk Management Activities

Because of the Not Approvable action, there are no recommendations for post-marketing risk management activities.

- Recommendation for other Postmarketing Study Commitments

Because of the Not Approvable action, there are no recommendations for post-marketing study commitments.

- Recommended Comments to Applicant

The following comments should be conveyed to the Applicant:

[Redacted text block containing multiple lines of horizontal lines]

b(4)

b(4)

b(4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sally Seymour
5/30/2008 10:14:30 AM
MEDICAL OFFICER