CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-114/S006

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMORANDUM

DATE: August 21, 2000

TO: NDA 20-114

/S/ /S/

FROM: Badrul A. Chowdhury, MD, PhD
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

8/24/00

SUBJECT: Secondary medical review of Astelin® (azelastine hydrochloride) Nasal Spray, 137 mcg, efficacy supplement for the treatment of symptoms of vasomotor rhinitis in adults and children 12 years of age and older

CC: HFD-570: Meyer, Lee, Trout

Administrative

NDA 21-165 efficacy supplement for azelastine nasal spray was submitted by Wallace Laboratories on November 10, 1999. The user fee goal date for action on this application is September 15, 2000. Azelastine nasal spray was approved for treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and older on November 11, 1996. On May 30, 2000, a pediatric efficacy supplement for ages 5 to 11 years was approved. The approved SAR doses for patients 12 years and above is 2 sprays (137 mcg/spray) in each nostril twice daily, and for patients 5 to 11 years of age is 1 spray in each nostril twice daily. The sponsor now submits this efficacy supplement to seek approval for treatment of symptoms of vasomotor rhinitis (VMR) for patients 12 years and above. The proposed dose is 2 sprays (137 mcg/spray) in each nostril twice daily.

There are no pharmacology, toxicology, biopharmaceutics, or chemistry issues in this submission.

Clinical studies

The sponsor has submitted efficacy and safety data from two pivotal studies conducted in 426 patients with VMR. These studies had essentially the same design. They are briefly reviewed in the subsequent sections. In addition, the sponsor has submitted results from two supporting studies. The supporting studies are not commented upon in this memorandum. Detail review of the clinical studies can be found in Dr. Lee's medical review.

Study 335: Efficacy and safety study

This was a two-arm, 1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of azelastine nasal spray versus placebo. The study enrolled 12 to 65 year old (overall mean age 40.3 years) patients with VMR in 15

US centers during the winter and early spring of 1999. To be eligible, patients were required to have VMR for at least one year, negative skin test to indoor and outdoor aeroallergens, positive skin test to histamine (i.e., able to react to allergen), negative nasal cytology for eosinophils, and negative sinus x-ray.

The study had a one-week placebo run-in baseline period followed by a three-week double-blind treatment period. Follow-up visits were at days 7 and 21. Study drug was administered daily in the morning and in the evening at approximately the same time each day. Efficacy assessment was primarily based on patients scoring of four nasal symptoms (congestion, sneezing, rhinorrhea, and postnasal drip) on 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) recorded daily in diary card in the morning and in the evening before dosing. Scoring was reflective of the status over previous half-a-day. The primary efficacy endpoint was the difference between the total VMR symptom score for the one-week baseline period and the three-week treatment period. Safety variables included adverse event recording, vital signs, physical examination, urinalyses, CBC, and clinical chemistry.

A total of 223 patients were randomized, approximately equally to the two treatment groups. Approximately 90% of patients completed the study. The ITT population, defined as patients who received at least one dose of study drug and had baseline and some follow-up data, included 218 patients. Results of change from baseline in the patient assessed total VMR symptoms score averaged over the three-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 1. The results support the efficacy of azelastine for the treatment of symptoms of VMR. Overall (weeks 1-3) symptom score change from baseline was statistically superior for azelastine compared to placebo. The effect size was relatively large. Azelastine maintained the effect over the three weeks of treatment, however, the difference from placebo was not statistically significant at week 3 because of a large placebo response towards the end of the study. The differences for individual symptom scores also favored azelastine.

Table 1. Change from baseline in patient assessed total VMR symptom scores

Evaluation period	Treatment (n)	Baseline score	Change from Baseline	P-value
Overall (Weeks 1-3)	Azelastine (n=111) Placebo (n=107)	6.51 6.54	1.54 0.84	0.002
Overall (Week 1)	Azelastine (n=111) Placebo (n=107)	6.51 6.54	1.13 0.26	0.001
Overall (Week 2)	Azelastine (n=111) Placebo (n=107)	6.51 6.54	1.65 1.14	0.029
Overall (Week 3)	Azelastine (n=111) Placebo (n=107)	6.51 6.54	1.92 1.41	0.120
Congestion (Weeks 1-3)	Azelastine (n=111) Placebo (n=107)	2.11 2.04	0.36 0.19	
Sneezing (Weeks 1-3)	Azelastine (n=111) Placebo (n=107)	0.85 0.85	0.25 0.08	
Rhinorrhea (Weeks 1-3)	Azelastine (n=111) Placebo (n=107)	1.49 1.58	0.48 0.31	
Postnasal drip (Weeks 1-3)	Azelastine (n=111) Placebo (n=107)	2.07 2.08	0.44 0.26	
Source: vol 44.1, pages 8.64, 8.87, 8.90, 8.104				

Azelastine was well tolerated in this study. Adverse events reported more frequently by azelastine treated patients than placebo treated patients were taste perversion (15% vs 4%), dysesthesia (10% vs 4%), pharyngitis (9% vs 7%), rhinitis (7% vs 3%), sinusitis (4% vs 1%), somnolence (2% vs 0%), and diarrhea (2% vs 0%). Eight patients in azelastine group had elevated AST and ALT as compared to none in the placebo treated patients. Two patients had over 3-fold elevation of ALT and AST on treatment. On follow-up about 10 days later, the values decreased, but were still higher than baseline. The transaminase values are discussed further in sections 8.1.4.7.g and 10.3.6 of Dr. Lee's review.

Study 336: Efficacy and safety study

This study was a replicate of study 335 with same entry criteria, study design, efficacy and safety measures. A total of 203 patients (overall mean age 41.1 years) with VMR from 15 US centers during the winter and early spring of 1999 were randomized approximately equally to the two treatment groups. Approximately 90% of patients completed the study. The ITT population included 196 patients. Results of change from baseline in the patient assessed total VMR symptoms score averaged over the three-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 1. The results support the efficacy of azelastine for the treatment of symptoms of VMR. Overall (weeks 1-3) symptom score change from baseline was statistically superior for azelastine compared to placebo. The effect size was relatively large. Azelastine maintained the effect over the three weeks of treatment. Unlike the previous study, the differences were statistically different for all three treatment weeks. All individual symptom scores also favored azelastine.

Table 2. Change from baseline in patient assessed total VMR symptom scores

Evaluation period	Treatment (n)	Baseline score	Change from Baseline	P-value
Overall (Weeks 1-3)	Azelastine (n=97)	6.52	1.54	[redacted]
	Placebo (n=199)	6.65	0.88	
Overall (Week 1)	Azelastine (n=97)	6.52	1.10	[redacted]
	Placebo (n=99)	6.65	0.62	
Overall (Week 2)	Azelastine (n=91)	6.52	1.72	[redacted]
	Placebo (n=95)	6.65	0.92	
Overall (Week 3)	Azelastine (n=91)	6.52	1.93	[redacted]
	Placebo (n=94)	6.65	1.04	
Congestion (Weeks 1-3)	Azelastine (n=97)	2.08	0.37	
	Placebo (n=99)	2.05	0.24	
Sneezing (Weeks 1-3)	Azelastine (n=97)	0.82	0.21	
	Placebo (n=99)	0.91	0.13	
Rhinorrhea (Weeks 1-3)	Azelastine (n=97)	1.52	0.48	
	Placebo (n=99)	1.61	0.26	
Postnasal drip (Weeks 1-3)	Azelastine (n=111)	2.10	0.48	
	Placebo (n=107)	2.08	0.26	
Source: vol 44.4, pages 8.966, 8.986, 8.988, 8.991				

Azelastine was well tolerated in this study. Adverse events reported more frequently by azelastine treated patients than placebo treated patients were taste perversion (24% vs 1%),

dysesthesia (6% vs 3%), somnolence (5% vs 2%), rhinitis (4% vs 2%), epistaxis (4% vs 2%), back pain (3% vs 1%), urinary tract infection (3% vs 0%), paresthesia (2% vs 0%), dry mouth (2% vs 0%), and thirst (2% vs 0%). Unlike the previous study, changes in transaminases were equal in the two treatment groups.

Efficacy assessment

The two clinical studies submitted in this efficacy supplement support the efficacy of azelastine nasal spray at a dose of two sprays each nostril twice daily for treatment of VMR symptoms in patients 12 years and above. Azelastine nasal spray has a bitter taste, which could have unblinded the study. However, the large effect size seen in both studies, and consistency of the results partially mitigate this concern. Further, the bitter taste could have biased the study either way, and not necessarily favored azelastine.

VMR is considered to be a sub-type of nonallergic rhinitis. Examples of some other sub-types of nonallergic rhinits include infectious rhinitis, rhinitis medicamentosa, atrophic rhinitis, and nonallergic rhinitis with eosinophilia. The term VMR has been used loosely to describe patients with perennial nonallergic rhinitis whose symptoms are associated with changes in temperature, relative humidity, alcohol, odors, bright light, or hot spicy food. The symptoms consist mainly of nasal obstruction and rhinorrhea. Sneezing and pruritus is less common. Although the term implies increased neural efferent traffic to the blood vessels supplying the nasal mucosa, this has never been proven[1].

In the studies submitted in this application, the investigators recruited patients with VMR, and excluded patients with allergic rhinitis and other forms of rhinitis. As expected, patients recruited in the studies were older than what is typically seen in allergic rhinitis clinical studies, and sneezing was not a major problem at baseline (Table 1, Table 2). Therefore, label claims relating to this efficacy supplement should specifically refer to VMR.

The mechanism of action of azelastine nasal spray in the treatment of VMR is unclear. It is unlikely to be solely from its H1 antihistamine property. Anticholinergic effects of azelastine may contribute to the observed effect. Nevertheless, the clinical studies demonstrated that azelastine was effective for control of VMR symptoms. Some other first-generation H1 antihistamines alone or in combination with decongestants also carry the VMR and/or nonallergic rhinitis indication. These antihistamines are chlorpheniramine, brompheniramine, cyproheptadine, and promethazine. Three nasal steroids - Flonase Nasal Spray, Rhinocort Nasal Inhaler, and Vancenase AQ Nasal Spray - are also approved for VMR and/or nonallergic rhinitis. Unfortunately, in some of these labels, the terms VMR and nonallergic rhinitis are used interchangeably. Atrovent nasal spray 0.03% is approved for relief of rhinorrhea associated with nonallergic perennial rhinitis.

---

[1] Druce HM. Allergic and nonallergic rhinitis. In: Allergy Principles and Practice, 5 th edn, Mosby, St. Louis, 1998: 1005-1016

Safety assessment

The safety of azelastine nasal spray is supported by the results of the two pivotal clinical studies, two other supporting studies, sponsor's summary of literature survey, and safety updates of azelastine nasal spray. Further the dose proposed is same as the approved SAR dose for the same age group. The adverse events seen in the clinical studies are typical of this class of drug. Elevation of transaminase seen in one study was not borne out in the other study. Dr. Lee conducted a search of the AERS database that revealed only two cases of elevated transaminases over the three-and-a-half year of marketing of azelastine in US. Both the cases were not convincing for a causal relationship. The cases are discussed in section 10.3.6 of Dr. Lee's review. Dr. Himmel's original azelastine nasal spray NDA review (NDA 20-114, July 19, 1993, pages 70 and 71) mentions elevated AST and ALT observed in clinical studies. The current product label of azelastine nasal spray already contains a statement on the rare occurrences of transaminase elevation.

[ ]

Data integrity

Data integrity in the clinical studies was verified by DSI audit of two investigator's sites (Dr. William Berger, Mission Viejo, CA; and Dr. Jonathan Matz, Baltimore, MD). These sites were chosen based on their contribution to the clinical program. DSI investigators identified some minor deficiencies, however, the investigators concluded that data from both sites were acceptable.

Recommendation

From a clinical standpoint this NDA is recommend an APPROVAL action. Efficacy and safety of azelastine nasal spray at a dose of two sprays each nostril twice daily is supported by the clinical studies and other documents submitted in the application. Labeling changes will be negotiated with the sponsor before the due date.

AUG 25 2000

Divfile

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Number:	20-114, SE5-006	**Application Type:**	NDA
Sponsor:	Wallace Laboratories	**Proprietary Name:**	Astelin® Nasal Spray
Category of Drug:	H_1 receptor antagonist	**USAN Name:**	Azelastine hydrochloride
		Route of Administration:	Nasal spray
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	8/21/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type, Comments:
N20-114, SE5-006	11/10/99	11/15/99	Efficacy supplement, 26 volumes
N20-114, P-011	8/27/99	8/31/99	Periodic safety update, 5/1/99-7/31/99
N20-114, P-012	11/22/99	11/23/99	Periodic safety update, 8/1/99-10/31/99
N20-114, C	1/28/00	1/31/00	Response to IR, electronic copy of label
N20-114, BM	2/11/00	2/14/00	Response to IR, subset analyses
N20-114, BM	7/13/00	7/14/00	Response to IR, case report forms

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:
N20-114, SE1-005	6/11/99	Efficacy supplement	Pediatric efficacy supplement

REVIEW SUMMARY:

This submission is an efficacy supplement for Astelin® (azelastine hydrochloride) Nasal Spray. The sponsor is Wallace Laboratories. The proposed indication is the treatment of the symptoms of vasomotor rhinitis in adults and children 12 years of age and older. The proposed dose is 2 sprays (137 mcg/spray) each nostril twice daily. The efficacy of azelastine nasal spray is supported by the results of the two pivotal US controlled clinical studies, Study 335 and 336. Both Study 335 and Study 336 showed that azelastine was statistically superior to placebo for the primary efficacy endpoint, the patient-recorded Total Vasomotor Rhinitis Symptom Score (TVRSS) over a three week treatment period. Individual symptom scores for rhinorrhea, sneezes, nasal congestion, and postnasal drip were superior for azelastine compared with placebo for the overall 3 week period and for Weeks 1, 2, and 3. The safety of azelastine nasal spray is supported by the results of the two pivotal US controlled clinical studies, Study 335 and 336, and foreign Study 338. AEs were more common in azelastine-treated patients than in placebo-treated patients. AEs occurring most frequently and in more than 2% of azelastine-treated patients were taste perversion, headache, dysesthesia, rhinitis, epistaxis, sinusitis, and somnolence. There were no SAEs or deaths in any of the clinical studies included in this submission. Withdrawals and data from vital signs or physical examination from studies included in this application do not reveal any new safety signals. Previously submitted periodic AE reports for 5/1/99 through 7/31/99 and 8/1/99 through 10/31/99 were reviewed and revealed no new safety signal. This reviewer recommends this application for approval.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION:

N drive location:

New Clinical Studies:	**Clinical Hold:**	**Study May Proceed:**	
NDA, Efficacy/Label Supplement is:	**Fileable:**	**Not Fileable:**	**Approvable: X**

SIGNED:

Medical Reviewer: /S/ **Date:** 8/25/00

Medical Team Leader: /S/ **Date:** 8/25/00

1. TABLE OF CONTENTS

2. EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1. Background and Administrative Issues

This submission is an efficacy supplement for Astelin® (azelastine hydrochloride) Nasal Spray. The sponsor is Wallace Laboratories. The proposed indication is the treatment of the symptoms of vasomotor rhinitis in adults and children 12 years of age and older. The proposed dose is 2 sprays (137 mcg/spray) each nostril twice daily [Volume 44.1, cover letter].

Azelastine hydrochloride is a phthalizinone derivative with histamine H_1-receptor antagonist activity. It is currently is marketed in the United States as Astelin® Nasal Spray, a 0.1% nasal spray solution administered via a pump spray bottle which delivers 0.137 mg of azelastine per spray, equivalent to 0.125 mg of azelastine base [Volume 44.1, page 02.2].

The application was received on November 15, 1999. The deadline for Agency action on this application is September 15, 2000.

2.2. Clinical Program

The sponsor seeks Agency approval to market this product for the treatment of the symptoms of vasomotor rhinitis in adults and children 12 years of age and older. The sponsor has submitted two pivotal US controlled clinical studies, Study 335 and 336. These studies had the same design. Both were multicenter, randomized, double-blind, placebo-controlled, parallel group studies. The sponsor submitted an article from the published literature describing a small open label, Japanese study of the effect of azelastine HCl, 1 mg po three times daily on the symptoms of vasomotor rhinitis, Study 337. The sponsor also submitted a European multicenter, randomized, double-blind, placebo-controlled, parallel group study of azelastine nasal spray in patients with vasomotor rhinitis, Study 338.

2.3. Efficacy

The efficacy of azelastine nasal spray in supported by the results of the two pivotal US controlled clinical studies, Studies 335 and 336. These efficacy results of these two studies are described below.

Study 335 was a three-week, randomized, double-blind, parallel-group, Phase 3 study performed in 15 US centers. The objective of this study was to assess the safety and efficacy of Astelin® Nasal Spray (azelastine HCl), 137 mcg, versus placebo nasal spray in patients with symptoms of vasomotor rhinitis. Azelastine was statistically superior to placebo for the primary efficacy endpoint, the patient-recorded Total Vasomotor Rhinitis Symptom Score (TVRSS) over the three week treatment period. An absolute effect size of 12.8% was seen in the primary efficacy endpoint for azelastine-treated patients. Individual symptom scores for rhinorrhea, sneezes, nasal congestion, and postnasal drip were superior for azelastine compared with placebo for the overall 3 week period and for Weeks 1, 2, and 3. The patient global assessment of therapeutic effectiveness at the end of treatment showed little difference between treatment groups.

Study 336 was a three-week, randomized, double-blind, parallel-group, Phase 3 study performed in 15 US centers. The objective of this study was to assess the safety and efficacy of Astelin® Nasal Spray (azelastine HCl), 137 mcg, versus placebo nasal spray in patients with symptoms of vasomotor rhinitis. Azelastine was statistically superior to placebo for the primary efficacy endpoint, the Total Vasomotor Rhinitis Symptom Score (TVRSS), over the three week treatment period. An absolute effect size of 13.6% was seen in the primary efficacy endpoint for azelastine-treated patients. Improvement in the TVRSS was greater for azelastine than placebo at the end of Weeks 1, 2, and 3. Individual symptom scores for rhinorrhea, sneezes, nasal congestion, and postnasal drip were superior for azelastine compared with placebo for the overall 3 week period and for Weeks 1, 2, and 3. A higher percentage of azelastine-treated patients than placebo-treated patients indicated they would continue their study medication if it was commercially available.

Studies 337 and 338 do not provide additional efficacy information for azelastine nasal spray and the treatment of the symptoms of vasomotor rhinitis. The efficacy variables were poorly defined and study results are not clearly presented.

Both pivotal clinical studies support the efficacy of azelastine nasal spray in the treatment of symptoms of vasomotor rhinitis. Although these studies were overpowered to detect the amount of difference specified in the primary efficacy endpoint, and possible problems with blinding were present, the effect sizes were large, 12.8% and 13.6% in Studies 335 and 336, respectively. It is likely that a statistically significant difference between treatment groups would have been achieved even if there had not been overenrollment.

2.4. Safety

The safety of azelastine nasal spray in supported by the results of the two pivotal US controlled clinical studies, Study 335 and 336, foreign Studies 337 and 338, the sponsor's Summary of Safety and literature survey, and periodic safety updates for 5/1/99 through 7/31/99 and 8/1/99 through 10/31/99. The proposed dose is the same as the approved dose for SAR for the same ages, and therefore, safety data from prior studies leading to approval of the SAR indication also supports the safety of this product. The safety data included in this application supports the safety of azelastine nasal spray in the treatment of the symptoms of allergic rhinitis.

Treatment exposure in the studies included in this application was adequate to assess safety. AEs were more common in azelastine-treated patients than in placebo-treated patients. AEs occurring most frequently and in more than 2% of azelastine-treated patients were taste perversion, headache, dysesthesia, rhinitis, epistaxis, sinusitis, and somnolence. Taste perversion, headache, rhinitis, and somnolence are noted in the current product labeling. Sinusitis occurred more frequently in azelastine-treated patients than in placebo-treated patients. There were no SAEs or deaths in any of the clinical studies included in this submission. Withdrawals and data from vital signs and physical examination from studies included in this application do not reveal any new safety signals. ECGs were not performed in studies included in this application. Previously submitted periodic AE reports for 5/1/99 through 7/31/99 and 8/1/99 through 10/31/99 were reviewed and revealed no new safety signal.

Review of the safety data in this application identifies no other safety concerns. The safety data included in this application supports the safety of azelastine nasal spray in the treatment of the symptoms of vasomotor rhinitis.

2.5. Special Populations

There was no difference in efficacy between men and women for the primary efficacy endpoint in either of the two pivotal controlled clinical studies. The majority of the patients in both clinical studies were Caucasian. The small number of non-Caucasians precluded any meaningful treatment by race analysis of efficacy. Very small numbers of patients in studies submitted in this NDA were over the age of 65 years, and none were under the age of 12 years. Small numbers of patients in these age groups preclude a subgroup analysis of efficacy. Ten patients ages 12-15 were enrolled in the two pivotal studies. Analysis of efficacy in this age group showed no difference between azelastine and placebo groups. The lack of difference may represent either a lack of efficacy in this age group, but may more likely reflect an insufficient sample size to detect a difference between treatment groups, as there is no indication that either the medication or the disease process are different in this age group than others.

Women had higher rates of taste perversion, headache, dysesthesia, rhinitis, epistaxis, sinusitis, and somnolence than men in the two pivotal clinical studies. Men and women had equal rates of pharyngitis. The majority of the patients in both clinical studies were Caucasian. The small number of non-Caucasians precluded any meaningful analysis of safety by race. Very small numbers of patients in studies submitted in this NDA were over the age of 65 years, and none were under the age of 12 years. Small numbers of patients in these age groups preclude a subgroup analysis of safety in these age groups. Ten patients ages 12-15 were enrolled in the two pivotal studies. AEs were of similar types to those reported by the entire azelastine-treated group. Analysis of AE frequency in patients ages 12-15 was not possible because of the small numbers.

2.6. Recommended Regulatory Action

The efficacy of azelastine nasal spray in the treatment of the symptoms of vasomotor rhinitis is supported by the two controlled clinical studies 335 and 336. The large effect sizes noted in the pivotal studies mitigate the concerns of blinding and overpowering. The safety of azelastine nasal spray is supported by this application. Future AEs reports should be monitored for additional instances of sinusitis and elevated AST and/or ALT, however.

Subgroup analysis did not show efficacy in patients 12 to 16 years of age, but this finding likely reflects insufficient statistical power to demonstrate efficacy. Children down to age 12 years of age were studied as part of the population in clinical trials for all intranasal medications approved in the US for the treatment of vasomotor or nonallergic rhinitis. A list of these medications is presented in Table 2.1.

Table 2.1 Intranasal medications approved in the US for the indication of vasomotor or nonallergic rhinitis.

Medication [Reference]	Action, class	Dosage form	Ages
Atrovent 0.03% [NDA 20-393 division files]	Anticholinergic*	Pump nasal spray solution	≥ 6 years*
Beconase AQ [NDA 19-389 division files]	Corticosteroid	Pump nasal spray suspension	≥ 6 years
Flonase [NDA 20-121 division files]	Corticosteroid	Pump nasal spray suspension	≥ 4 years
Rhinocort Nasal Inhaler** [NDA 20-233 division files]	Corticosteroid	Pressurized inhaler, nasal spray suspension	Adults
Vancenase AQ [NDA 19589, 19389 division files]	Corticosteroid	Pump nasal spray suspension	≥ 6 years
Vancenase AQ Double Strength [NDA 20-469 division files]	Corticosteroid	Pump nasal spray suspension	≥ 6 years

*Indicated for the symptomatic relief of rhinorrhea, but not nasal congestion, sneezing, or postnasal drip.
**Rhinocort Aqua Nasal Spray is not approved for treatment of vasomotor or nonallergic rhinitis.

The efficacy and safety of azelastine nasal spray was demonstrated in the pivotal studies in this application, and supported by the two foreign studies, the sponsor's Summary of Safety, periodic spontaneous report updates, and by prior safety data. This reviewer recommends this application for approval.

3. MATERIAL REVIEWED AND CONDUCT OF THE REVIEW

The following items were included in this application:

- Clinical studies
  - This application includes clinical studies, Studies 335, 336, 337, and 338. Studies 335 and 336 are pivotal controlled clinical studies. Study 337 is a publication from the literature on the use of azelastine tablets given orally in the treatment of symptoms of allergic rhinitis. Study 338 is a report of a foreign Phase 3 clinical study. These studies are summarized in Table 3.1. More detailed descriptions of these studies are found in subsequent sections.
- Sponsor's Summary of Efficacy and Summary of Safety
- Literature review
- Periodic AE reports for 5/1/99 through 7/31/99 and 8/1/99 through 10/31/99
- Proposed product labeling

Table 3.1 Summary of studies, NDA 20-114, vasomotor rhinitis efficacy supplement

U.S. Controlled Clinical Studies					
Study Number	**Study Type**	**Treatment Groups**	**Duration of treatment**	**Design**	**Number of subjects**
335	Pivotal efficacy and safety study	Astelin® Nasal Spray, 2 sprays each nostril BID, and placebo	3 weeks	Double-blind, randomized, placebo-controlled, parallel group, 15 centers	223
336	Pivotal efficacy and safety study	Astelin® Nasal Spray, 2 sprays each nostril BID, and placebo	3 weeks	Double-blind, randomized, placebo-controlled, parallel group, 15 centers	203
Other Studies					
Study Number	**Study Type**	**Treatment Groups**	**Duration of treatment**	**Design**	**Number of subjects**
337	Proof of concept Japan	Azelastine 1 mg tablets, 1 tab po TID	2 weeks	Open label, 1 center	11
338	Efficacy and safety France	Azelastine nasal spray, 1 spray each nostril TID, and placebo	15 days	Double-blind, randomized, placebo-controlled, parallel group, 19 centers	89

4. CHEMISTRY/MANUFACTURING AND CONTROLS

Astelin® (azelastine hydrochloride) Nasal Spray, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is $C_{22}H_{24}ClN_3O \cdot HCl$. Astelin® Nasal Spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.

After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). Each bottle can deliver 100 metered sprays. [Volume 44.1, page 02.2]

For US clinical Studies 335 and 336, study treatment, both azelastine and placebo, was packaged in high-density polyethylene (HDPE) bottles fitted with a screw cap, with a separate metered-dose spray pumps for each bottle. One spray delivered a mean of 0.137 mL of azelastine or placebo. One spray of active treatment delivered 137 mcg of azelastine HCl. Placebo was identical to active drug with the exception of the active ingredient.

The drug formulation for azelastine nasal spray for US pivotal clinical studies 335 and 336, and French study 338 was identical to the currently US approved product. The delivery system for azelastine nasal spray for US pivotal clinical studies 335 and 336 was identical to the currently approved product. The delivery system for French study 338 has been shown to have comparable performance to the pump used in the currently approved US product. [Correspondence, 7/24/00, Wallace Laboratories, G. Hemsworth, Ph.D.]. Study 337 used a 1 mg tablet formulation of azelastine HCl [Volume 44.1, page 08.10].

5. ANIMAL PHARMACOLOGY/TOXICOLOGY

No new preclinical pharmacology or toxicology studies were conducted in support of this application [Volume 1.1, page 38].

6. CLINICAL BACKGROUND

Astelin® Nasal Spray was approved in November 1996 for the treatment the symptoms of seasonal allergic rhinitis (SAR). The recommended dose for treatment of the symptoms of SAR in adults and children 12 years of age and older is 2 sprays each nostril twice daily and ages 6-12 years for the treatment of the symptoms of SAR at the dose of 1 spray each nostril twice daily. An ophthalmologic form of azelastine, Optivar®, azelastine HCl 0.05% ophthalmic solution, NDA 21-127, was approved in the US on 5/22/00.

The sponsor's proposed indication for this product is vasomotor rhinitis [Volume 44.1, page 02.4]. The sponsor tends to use the terms vasomotor rhinitis and nonallergic rhinitis interchangeably. There is some conflict in medical literature on the proper nomenclature for patients who have sporadic or persistent perennial symptoms of rhinitis that do not result from IgE-mediated events[1,2]. There is no universally accepted definition for perennial nonallergic rhinitis, and no simple mechanism has been demonstrated in this condition[1]. In a broad sense, all patients who do not have an allergic etiology for their symptoms could be thought of as having "nonallergic rhinitis." This classification is broad, and includes other specific conditions such as nonallergic rhinitis not associated with eosinophilia, nonallergic rhinitis with eosinophilia syndrome (NARES), aspirin triad, and infectious rhinitis. The classification of chronic rhinitis is presented in Table 6.1. This working classification was

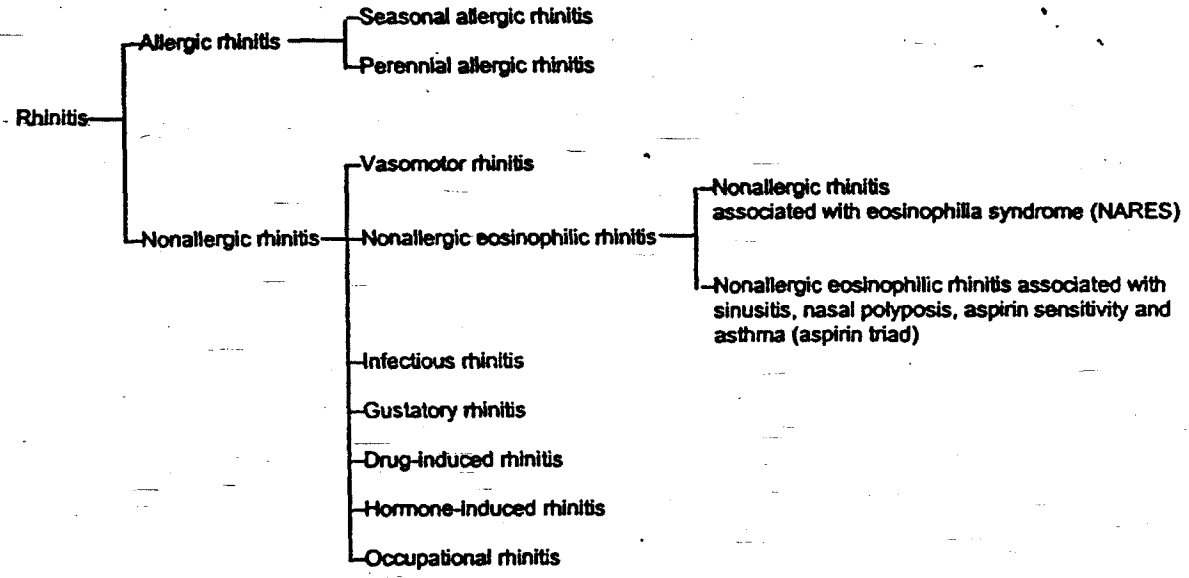
[1] Druce HM. Allergic and nonallergic rhinitis. In: Allergy Principles and Practice, 5th edition, Mosby, St. Louis, 1998: 1005-1016

[2] Philip G, Togias AG. Nonallergic rhinitis. Pathophysiology and models for study. Eur Arch Otorhinolaryngol 1995;252(Suppl. 1):S27-S32.

compiled with information from a number of references.[1,2,3,4,5,6] Vasomotor rhinitis is used to describe patients with symptoms that may be produced from temperature changes, odors or fragrances, smoke, or stress. Although this term is frequently used to describe patients who have nasal symptoms that result from environmental changes, increased neural traffic to the blood vessels of the nasal mucosa have not been demonstrated.

The pivotal clinical studies included in this application have enrolled patients with a history and diagnosis of vasomotor rhinitis for more than one year who had positive histamine skin tests, negative allergen skin tests and nasal smear for eosinophils, and negative sinus X-rays. For this reason, the term "vasomotor rhinitis" will be used in this review for studies included in this review and for product labeling.

Table 6.1 Classification of chronic rhinitis



Treatment for vasomotor rhinitis is empiric and directed at the relief of symptoms. Various medications that have been approved for treatment of nonallergic rhinitis are displayed in Table 6.2. These medications include oral antihistamines, oral decongestants, oral antihistamine/decongestant combinations, as well as anticholinergic and corticosteroid nasal sprays. The mechanism of action of antihistamines in the treatment of vasomotor rhinitis is unclear, but may be the result of anticholinergic activity.

[3] Dykewicz MS, Fineman S. Diagnosis and management of rhinitis: Parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol 1998;81:463-518.
[4] Mullarkey MF. Eosinophilic nonallergic rhinitis. J Allergy Clin Immunol 1988;82:941-949.
[5] Middleton E. Chronic rhinitis in adults. J Allergy Clin Immunol 1988;81:971-975.
[6] Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome). J Allergy Clin Immunol 1981;67:253-262.

Table 6.2 Medications approved for the indications of vasomotor rhinitis or nonallergic rhinitis [Physicians Desk Reference, 2000, http://www.pdrel.com]

Trade name	Generic name	Class	Route and form
Alumadrine	Acetaminophen, Phenylpropanolamine HCl, Chlorpheniramine maleate	Analgesic/ Antihistamine/ Decongestant	Oral tablet
Bromfed, Bromfed-PD	Brompheniramine maleate, Pseudoephedrine HCl	Antihistamine/ Decongestant	Oral capsule
[redacted]			
Periactin	Cyproheptadine HCl	Antihistamine	Oral tablets
Phenergan	Promethazine HCl	Antihistamine	Oral syrup, tablets Rectal suppository
Atrovent 0.03%	Ipratropium bromide	Anticholinergic	Nasal solution, Manual pump spray
Beconase AQ	Beclomethasone dipropionate	Corticosteroid	Nasal suspension, Manual pump spray
Flonase	Fluticasone propionate	Corticosteroid	Nasal suspension, Manual pump spray
Rhinocort Nasal Inhaler®	Budesonide	Corticosteroid	Nasal suspension, Pressurized meter dose inhaler
Vancenase AQ Vancenase AQ Double Strength	Beclomethasone dipropionate	Corticosteroid	Nasal suspension, Manual pump spray

6.1. Human Pharmacology, Pharmacokinetics, and Pharmacodynamics

No new preclinical pharmacology or toxicology studies were conducted in support of this application.

6.2. Foreign Experience

Azelastine HCl in not approved for the treatment of vasomotor rhinitis or nonallergic rhinitis in any country where it is currently marketed [Volume 1.184, cover letter].

7. DESCRIPTION OF CLINICAL DATA SOURCES

Table 7.1 lists all IND and NDA applications referred to in the sponsor's application.

Azelastine INDs and NDAs [Volume 44.1, page not numbered]

Document type	Number	Subject	Dosage form	Owner
[redacted]				

8. CLINICAL STUDIES

8.1. Study 335: A randomized, double-blind, placebo-controlled, parallel-group study of the safety and efficacy of Astelin® Nasal Spray (azelastine HCl) 137 mcg in the treatment of subjects with symptoms of vasomotor rhinitis

First patient enrolled: 2/8/99
Last observation: 5/28/99
Study report dated: 11/2/99

8.1.1. Summary and reviewer's conclusion of study results

This was a three-week, randomized, double-blind, parallel-group, Phase 3 study performed in 15 US centers. The objective of this study was to assess the safety and efficacy of Astelin® Nasal Spray (azelastine HCl), 137 mcg, versus placebo nasal spray in patients with symptoms of vasomotor rhinitis.

Azelastine was statistically superior to placebo for the primary efficacy endpoint, the patient-recorded Total Vasomotor Rhinitis Symptom Score (TVRSS) over the three week treatment period. An absolute effect size of 12.8% was seen in the primary efficacy endpoint for azelastine-treated patients. Improvement in the TVRSS was greater for azelastine than placebo at the end of Weeks 1, 2, and 3, although there was less drug effect noted at Week 3 because of improvement in the placebo group. Individual symptom scores for rhinorrhea, sneezes, nasal congestion, and postnasal drip were superior for azelastine compared with placebo for the overall 3 week period and for Weeks 1, 2, and 3. The patient global assessment of therapeutic effectiveness at the end of treatment showed little difference between treatment groups.

This study supports the efficacy of azelastine nasal spray in the treatment of symptoms of vasomotor rhinitis. Although the power calculation called for an enrollment of 160 patients to be able to detect a 10% difference in the primary efficacy endpoint between treatment groups, there were 223 patients randomized. This study was overpowered to detect the amount of difference specified in the primary efficacy endpoint. However, an effect size greater than 10% was observed, and it is likely that a statistically significant difference between treatment groups would have been achieved even if there had not been overenrollment. A deficiency in this study was impairment in blinding. Patients randomized to active drug would have been likely to taste a difference from the placebo drug given during the single blind baseline evaluation period, but placebo patients would not. As a result of this deficiency, the case for efficacy of the drug is less persuasive.

This study supports the safety of azelastine nasal spray. There was adequate exposure to study drug to assess safety. Adverse events (AEs) were slightly less frequent in azelastine-treated patients than in placebo-treated patients. AEs occurring more frequently in azelastine-treated patients than in placebo-treated patients included taste perversion, dysesthesia, pharyngitis, rhinitis, sinusitis, somnolence, and diarrhea. Bitter taste, somnolence, pharyngitis, and rhinitis are noted in current azelastine product information. There were no

deaths or serious adverse events in this study. There were no clinically significant changes in vital signs or body weight in patients in either azelastine or placebo groups. The types and frequency of physical exam abnormalities were similar in azelastine- and placebo-treated groups. Eight patients in the azelastine group and none in the placebo group developed elevated AST (SGOT) and/or ALT (SGPT) levels at the close of the study.

8.1.2. Objective/Rationale

The objective of this study was to assess the safety and efficacy of Astelin® Nasal Spray (azelastine HCl), 137 mcg, versus placebo nasal spray in patients with symptoms of vasomotor rhinitis [Volume 44.1, page 08.43].

8.1.3. Protocol

This three-week, randomized, double-blind, parallel-group, Phase 3 study was performed in 15 US centers. Up to 300 men and women, ages 12-65 years were to be randomized. Patients were to have a history and diagnosis of vasomotor rhinitis with a positive response to histamine skin test, a negative epicutaneous skin test to a panel of indigenous aeroallergens, and a nasal cytology examination that was negative for eosinophils [Volume 44.1, pages 08.43, 08.129].

Patients were screened for entry at Visit 1, and then began a seven day single-blind baseline evaluation period during which they received placebo nasal spray, two sprays in each nostril twice daily. Patients were to monitor their vasomotor rhinitis symptoms twice daily and assess and record their severity in a subject diary. Patients were required to meet adequate symptom severity score criteria for randomization to the study treatment period [Volume 44.1, pages 08.140-08.146]. The severity of vasomotor rhinitis symptoms was assessed using the four-point scales presented in Table 8.8.1.

Table 8.1.1. Vasomotor symptom scales [Volume 44.1, pages 08.142-08.143].

Nasal Congestion	
0	None. Symptom not present.
1	Mild. Symptom occurs up to one hour per half day which is noticeable and does not interfere with activity.
2	Moderate. Symptom occurs one to two hours per half day which is bothersome and interferes slightly with activity.
3	Severe. Symptom occurs more than two hours per half day which is very bothersome and interferes significantly with activity.
Sneezing	
0	None. Symptom not present.
1	Mild. Symptom occurs less than 5 times per half day.
2	Moderate. Symptom occurs 5 to 10 times per half day.
3	Severe. Symptom occurs more than 10 times per half day.

Rhinorrhea	
0	None. Symptom not present.
1	Mild. Symptom occurs less than 5 times per half day which is noticeable and does not interfere with activity.
2	Moderate. Symptom occurs 5 to 10 times per half day which is bothersome and interferes slightly with activity.
3	Severe. Symptom occurs more than 10 times per half day which is very bothersome and interferes significantly with activity.
Postnasal drip	
0	None. Symptom not present.
1	Mild. Symptom occurs up to two hours per half day which is noticeable and does not interfere with activity.
2	Moderate. Symptom occurs two to four hours per half day which is bothersome and interferes slightly with activity.
3	Severe. Symptom occurs more than four hours per half day which is very bothersome and interferes significantly with activity.

Randomization was performed at Visit 2, after the seven day baseline evaluation period. Patients were randomized to one of two double-blind treatment groups if they satisfied the criteria for minimum baseline symptom severity. The sum of individual vasomotor rhinitis symptom scores in the morning or the evening must have been ≥ 6 on four of the seven days. In addition, least two of the individual vasomotor rhinitis symptoms must have been scored 2 or 3 (moderate or severe) on the same four days [Volume 44.1, page 08.144].

Patients were dispensed study medication if they met the minimum baseline vasomotor rhinitis symptom scores. Patients were given either of the following two study treatments:

- Astelin® Nasal Spray (azelastine HCl), 137 mcg, two sprays in each nostril twice daily for three weeks
- Placebo nasal spray, two sprays in each nostril twice daily for three weeks

It should be noted that the benefit of blinding may have been lost with this study design because of the taste of azelastine. Bitter taste is commonly reported with azelastine (see Section 8.1.4.7.b. Adverse Events). At randomization, patients assigned to azelastine would be likely to notice a change in the taste of medication, but placebo patients would not. This loss of blinding decreases the confidence of conclusions from efficacy outcomes.

Patients were to continue to monitor their vasomotor rhinitis symptoms twice daily and assess and record their severity in a subject diary during the three-week treatment phase using the scales displayed in Table 8.1.1. Patients were also to record the identity, quantity, and frequency of concomitant medications used. Patients scored their symptoms for four treatment periods: Baseline (Days 1-7, Visits 1 to 2), Week 1 (Days 8-14, Visit 2-3), Week 2 (Days 15-21), Week 3 (Days 22-29). An outline of the study design is presented in Table 8.1.2. Evaluation periods are displayed in Table 8.1.3 [Volume 44.1, pages 08.140-08.146].

Table 8.1.2. Study outline, Study 335 [Volume 44.1, pages 08.53, 08.140-08.146]

Visit Number	Visit 1 Screening	Visit 2 Randomization	Visit 3 Interim	Visit 4 Final
Study day	1	8	15	29
Check inclusion/exclusion criteria	X	X	X	X
Informed consent	X			
Medical History	X			
Vital signs	X			X
Physical Exam, nasal examination	X			X
Histamine and aeroallergen skin test	X			
Nasal cytology for eosinophils	X			
Sinus X-ray	X			
Obtain blood and urine for labs	X			X
Pregnancy test for women	X			
Dispense symptom diary	X	X	X	
Dispense placebo nasal spray for baseline period	X			
Collect medication and review diary		X	X	X
Randomization		X		
Dispense study medications		X	X	
Patient evaluation of signs and symptoms	X	X	X	X
Patients' global evaluation				X
Check adverse events		X	X	X

Table 8.1.3. Evaluation periods

Evaluation period	Study days
Baseline period	1 to 7
Treatment period	8 to 28
Week 1	8 to 14
Week 2	15 to 21
Week 3	22-28

8.1.3.1. Inclusion criteria [Volume 44.1, pages 08.136-08.137]

Patients were to meet the following inclusion criteria:

1. Ages 12 to 65 years
2. Maintain a stable lifestyle while participating in the study
3. Outpatient with a history and diagnosis of vasomotor rhinitis for which no etiology could be established and symptomatic for more than one year
4. Positive histamine epicutaneous skin test
5. Negative skin test for mixed panel of allergens including cat dander, dust mites, indigenous mold/mold mix, and tree, grass, and weed pollen/ pollen mixes for area
6. Nasal cytology examination negative for eosinophils
7. No clinically significant nasal anatomic abnormalities
8. Normal sinus X-ray (Waters view)
9. Be male, or if female, non-gravid, non-nursing, non-childbearing potential or of childbearing potential who were to agree not to become pregnant during the study. Sexually active females of childbearing potential were to be actively practicing adequate birth control using a double-barrier method only. Abstinence was not accepted as a method of birth control.
10. Executed a written informed consent document prior to beginning the baseline period. Written consent of a parent or legal guardian was to be required for subjects under the legal age of consent
11. Individual from whom the investigator or study personnel would expect conscience cooperation over the duration of the study

Inclusion criterion 8 was amended on February 8, 1999 to better define the inclusion of females of childbearing potential:

8. Be male, or if female, non-gravid, non-nursing, or of non-childbearing potential. Females of childbearing potential were to agree not to become pregnant during the study and to practice adequate birth control (either oral, implant, or injectable contraceptives or at least two of the following [diaphragm or sponge], spermicide, or condom) [Volume 44.1 page 08.156].

8.1.3.2. Exclusion criteria [Volume 44.1, pages 08.137-138]

Patients were not to be enrolled into the study if they had any of the following exclusion criteria:

1. Were pregnant, lactating, nursing, or if of childbearing potential, refused to abide by the contraception stipulations in the inclusion criteria
2. Had an inability to use or tolerate nasal sprays
3. Experienced an episode(s) of acute sinusitis within 30 days of Visit 1
4. Had glaucoma, cancer, uncontrolled diabetes mellitus, acute respiratory infection (including the common cold), any systemic infection, any clinically significant hematologic, renal, endocrine (except controlled diabetes mellitus or postmenopausal symptoms), hepatic or gastrointestinal disease, and/or neuropsychiatric disorders with or without drug therapy
5. Had a history of epilepsy or seizures, excessive alcohol intake or drug addiction, coronary artery disease, uncontrolled hypertension, or other clinically significant cardiovascular disease
6. Had a history of food allergy
7. Have rhinitis medicamentosa secondary to over-the-counter (OTC) intranasal vasoconstrictor use
8. Were a current cocaine user
9. Had physical examination abnormality(ies) considered clinically significant and limiting to the study's conduct by the investigator
10. Had nasal surgery within three months of Visit 1
11. Used an antihistamine within seven days of Visit 1
12. Used inhaled and/or topical corticosteroids within 14 days of Visit 1
13. Used systemic (intramuscular, intravenous, or oral) corticosteroids within 30 days of Visit 1
14. Used intranasal cromolyn (Nasalcrom®) and/or optical cromolyn (Opticrom®) within 30 days of Visit 1
15. Were taking any medications which could cause drug-induced rhinitis:
    - ACE inhibitors
    - Reserpine
    - Guanethidine
    - Phentolamine
    - Methyldopa
    - Prazosin
    - Beta-blockers

- Chlorpromazine
- Aspirin
- Non-steroidal anti-inflammatory medication (NSAIDs)
- Oral, injectable or implant contraceptives

16. Had been treated with any investigational drug within 30 days of Visit 1

Exclusion criterion 15 was amended on February 8, 1999 to better allow use of oral, implant, or injectable contraceptives [Volume 44.1, page 08-165]:

17. Were taking any medications which could cause drug-induced rhinitis:
    - ACE inhibitors
    - Reserpine
    - Guanethidine
    - Phentolamine
    - Methyldopa
    - Prazosin
    - Beta-blockers
    - Chlorpromazine
    - Aspirin
    - Non-steroidal anti-inflammatory medications (NSAIDs)

8.1.3.3. Drug product and placebo [Volume 44.1, pages 08.51]

Study treatment, both azelastine and placebo, were packaged in high-density polyethylene (HDPE) bottles fitted with a screw cap, with a separate metered-dose spray pumps for each bottle. One spray delivered a mean of 0.137 mL of azelastine or placebo. One spray of active treatment delivered 137 mcg of azelastine HCl. Placebo was identical to active drug with the exception of the active ingredient. The description and lot number for study medications follow:

Medication	Strength	Lot number
Astelin Nasal Spray	0.1%	8L92N
Placebo Nasal Spray	NA	6801

The drug formulation and delivery system for azelastine was identical to the currently approved US product [Correspondence, 7/24/00, Wallace Laboratories, G. Hemsworth, Ph.D.].

8.1.3.4. Assessment of signs and symptoms

Patients were to assess the severity of individual vasomotor rhinitis symptoms twice daily, in the morning and in the evening, using the symptom scales displayed in Table 8.1.1. As can be observed in the symptom scales, assessment was based on the severity of their symptoms over the preceding one-half day (reflective). The individual symptom scores were recorded in the patient diary.

A total vasomotor rhinitis symptom score (TVRSS) was calculated by summing the average daily symptom scores for rhinorrhea, sneezes, nasal congestion, and postnasal drip for each

one week evaluation period, Baseline through Week 3, making up the three-week treatment period [Volume 44.1, pages 08-142-08.145].

8.1.3.5. Variables

Efficacy and safety variables for this study are described below.

8.1.3.5.a. Primary efficacy variable

The primary efficacy variable was the Total Vasomotor Rhinitis Symptom Score (TVRSS). The primary efficacy endpoint was the difference between the TVRSS for the one-week Baseline period and the average of the TVRSS for the three one-week evaluation periods. This was termed the "Overall" endpoint [Volume 44.1, page 08.60].

The primary efficacy endpoint was calculated in the following manner [Volume 44.1, pages 08.58-08.59, 08.85, 08.150-08.151, Volume 44.2, pages 08.315-08.316]:

- Weekly morning and evening mean symptom scores were calculated for each of the four individual symptoms (nasal congestion, sneezing, rhinorrhea, postnasal drip) for the one-week single-blind baseline evaluation period, and for each of the one-week evaluation periods making up the three-week treatment period.
- The weekly morning and evening mean individual scores were averaged to produce a mean TVRSS for each one-week evaluation period, both baseline and treatment.
- The mean TVRSS for each of the three treatment weeks were averaged to produce the overall TVRSS.
- The primary efficacy endpoint ("Overall") was the difference between the baseline TVRSS and the overall TVRSS.

The protocol states that the primary analysis was to be the intent-to-treat analysis based on all subjects with any response data. The sponsor also calculated the primary efficacy endpoint with a last observation carried forward approach, termed "Endpoint." This endpoint was not examined in this review in order to avoid imputing data to those who may have dropped out of the study early. This study was overpowered for the specified effect size, and there is no need to maximize the sample size by imputing data to dropouts.

8.1.3.5.b. Secondary efficacy variables

Secondary efficacy variables included reduction in individual symptom scores, percentage of study dropouts, and patient global assessment of therapeutic effectiveness. Individual symptom scores were evaluated in terms of reduction from baseline at each of the three evaluation periods, and Overall, as with the primary efficacy endpoint (see Section 8.1.3.5.a. Primary efficacy variables). Patient global assessment of therapeutic effectiveness was evaluated by means of the following question: "If the nasal spray study medication you received for the last three weeks was available commercially, would you continue to take it for the control of your symptoms of vasomotor rhinitis? Yes or No." [Volume 44.1, pages 08.146, 08.152].

8.1.3.5.c. Safety variables

Safety variables included AEs, VS, PE, CBC, chemistry, and urinalysis. ECGs were not performed [Volume 44.1, pages 08-151-08.152].

8.1.3.6. Statistical Considerations

ANOVA incorporating terms for treatment, center, and their respective interactions was used to compare treatment groups with respect to reduction in TVRSS and individual symptom scores. Categorical data procedures (chi-square) were used to evaluate differences between treatment groups for percentage of dropouts and patient global assessment of therapeutic effectiveness. All comparisons used two-sided tests [Volume 44.1, pages 08.61, 08.152].

An estimate of the number of subjects needed was based on earlier results from clinical studies in seasonal allergic rhinitis (SAR) conducted by Wallace Laboratories. The sponsor assumed a mean reduction in each of the symptoms of 22% for the azelastine group and of 12% for the placebo group. A standard deviation of 20% was assumed. Approximately 80 patients per treatment group would be required to have 80% power and two-sided alpha of 0.05 to detect a 10 point difference between treatment groups in reduction of symptom scores [Volume 44.1, page 08.153].

8.1.4. Results

8.1.4.1. Populations enrolled/analyzed

There were 343 patients screened for participation in this study. Of these 343 patients screened, 120 were not randomized. Reasons for patients failing to qualify for randomization included low symptom scores (32%, 38/120), abnormal sinus X-ray (21%, 25/120), positive allergen skin test (12%, 14/120). and administrative reasons such as loss to follow-up or withdrawal of consent (11%, 13/120) [Volume 44.1, pages 08.62, 08.74-08.75].

There were 223 patients randomized to study treatment with 113 in the azelastine group and 110 in the placebo group. It should be noted that the power analysis called for a total of 160 patients, 80 in each treatment group, to detect a 10% difference in reduction in symptom scores between treatment groups with the specified standard deviation, alpha, and beta. This study was therefore overpowered and the statistical significance of outcome differences between study groups is likely to be inflated.

There were five patients excluded from the intent-to-treat analysis because of the lack of data other than the baseline visit. These patients included two randomized to azelastine and three randomized to placebo [Volume 44.1, pages 08.79, 08.63].

Of the 223 patients randomized, 22 did not complete the study, with eight in the azelastine group and 14 in the placebo group. One patient in each treatment group was incorrectly randomized and was withdrawn before any study medication was taken. Reasons for noncompletion of the study are listed in Table 8.1.4. The most common reasons for noncompletion were protocol violation and treatment failure. The majority of protocol violations were for incorrect randomization because of inadequate baseline symptom score, pre-existing significant medical condition, or use of prohibited medications [Volume 44.19, pages 11.2133-11.2140]. Protocol violations are displayed in Table 8.1.5. The small number of protocol violations are not likely to significantly influence efficacy and safety conclusions from this study.

Table 8.1.4. Patient disposition [Volume 44.19, pages 11.2133-11.2140].

	Azelastine		Placebo		All patients	
	N	(%)	N	(%)	N	(%)
Number of patients randomized	113	(100)	110	(100)	223	(100)
Number of patients completing study	105	(92.9)	96	(87.3)	201	(90.1)
Number of patients discontinued*	8	(7.1)	14	(12.7)	22	(9.9)
Adverse event	1	(0.9)	2	(1.8)	3	(1.4)
Intercurrent illness	0	(0)	1	(0.9)	1	(0.5)
Loss to follow-up	1	(0.9)	1	(0.9)	2	(0.9)
Protocol violation*	3	(2.7)	6	(5.4)	9	(4.0)
Treatment failure	3	(2.7)	4	(3.6)	7	(3.1)

*Includes two patients who were randomized and did not start study medication, one in azelastine group and one in placebo group. See Table 8.1.5. [Teleconference, 7/11/00, G. Hemsworth, Ph.D.]

Table 8.1.5 Protocol violations [Volume 44.19, pages 11.2133-11.2140].

Center	Treatment	Subject number	Protocol violation
980004	Placebo	3	Hypothyroidism, incorrect randomization
980006	Placebo	41	Inadequate symptom score, incorrect randomization*
980006	Placebo	42	Hypothyroidism, incorrect randomization
980010	Azelastine	121	Took prohibited medication, NSAID
980010	Azelastine	125	Took prohibited medication
980011	Azelastine	145	Took prohibited medication, Tylenol PM
980014	Placebo	201	Inadequate symptom score, incorrect randomization*
980017	Placebo	261	No data after baseline
980017	Placebo	264	Hypothyroidism**, incorrect randomization

*Randomized, but never received double-blind medication [Telecon, 7/11/00, G. Hemsworth, Ph.D.]
**From Volume 44.18, page 11.2063

8.1.4.2. Baseline demographic and background characteristics

Demographics are presented in Table 8.1.6. The population studied was largely Caucasian. There were more females than males in the study. The mean age was approximately 40 years in both treatment groups. Both treatment groups had similar age distributions. There were only a few patients ages 12-15 years in both treatment groups. Treatment groups were similar in gender. There were slightly more Black patients in the azelastine treatment group, otherwise the race distribution was similar in treatment groups.

Table 8.1.6 Study 335, demographics [Volume 44.1, page 08.81, Volume 44.13, pages 11.1-11.8]

Characteristic	Azelastine N = 113		Placebo N = 110		Total N = 223	
Age, years	n	(%)	n	(%)	n	(%)
12-16	6	(5)	7	(6)	13	(6)
17-19	5	(4)	2	(2)	7	(3)
20-29	9	(8)	11	(10)	20	(9)
30-39	35	(31)	28	(25)	63	(28)
40-49	33	(29)	33	(30)	66	(30)
50-59	19	(17)	23	(21)	38	(17)
60-65	6	(5)	3	(3)	12	(5)
>65	0	(0)	0	(0)	0	(0)
Mean age	40.2		40.4		40.3	
SD	12.3		12.4		12.3	
Gender	n	(%)	n	(%)	n	(%)
Male	37	(33)	34	(31)	71	(32)
Female	76	(67)	76	(69)	152	(68)
Race	n	(%)	n	(%)	n	(%)
Caucasian	102	(90)	103	(94)	205	(92)
Black	9	(8)	2	(2)	11	(5)
Other	2	(2)	5	(4)	7	(3)

8.1.4.3. Protocol deviations

There were 32 patients with protocol deviations, with 13 in the azelastine group and 19 in the placebo group. The majority of protocol deviations were for use of prohibited medications, with 10 in the azelastine group and 15 in the placebo group. There were three protocol deviations in the azelastine group and seven in the placebo group for use of antihistamines, decongestants, sympathomimetics, or inhaled corticosteroids [Volume 44.1, pages 08.63, 08.80]. This finding provides some indirect support for the efficacy of azelastine.

8.1.4.4. Compliance

Compliance was determined by review of patient diary entries. These data are displayed 8.1.7. Patients were to record the time for each dose of study medication that was taken. Only 8.9% of azelastine-treated patients and 13.6% of placebo-treated patients received less than 20 days of the 21-day course of study medication. In the azelastine group, 77.9% of patients were treated for 20 to 22 days, and in the placebo group, 70.0% of patients were treated for 20 to 22 days. The duration of treatment was 23 to 29 days in 3.3% of the azelastine group and 16.4% of the placebo group. Treatment for more than the specified duration was a result of scheduling delays for follow-up visits [Volume 44.1, pages 08.68, 08.104]. In this reviewer's opinion, compliance was adequate to assess efficacy and safety.

Table 8.1.7. Patient compliance [Volume 44.1, page 08.104].

Duration of treatment	Azelastine n	(%)	Placebo n	(%)	Total n	(%)
0 to 19 days	10	(8.9)	15	(13.6)	25	(11.2)
20 days	3	(2.7)	5	(4.5)	8	(3.6)
21 days	46	(40.7)	39	(35.4)	85	(38.1)
22 days	39	(34.5)	33	(30.0)	72	(32.3)
23 to 29 days	15	(3.3)	18	(16.4)	33	(14.8)
Total	113	(100)	110	(100)	223	(100)

8.1.4.5. Use of concomitant medications

The use of concomitant medications was similar in the azelastine and placebo groups. Azelastine-treated patients used slightly less antihistamines, decongestants, nasal corticosteroids, or antihistamine or decongestant combinations than placebo-treated patients. These data are displayed in Table 8.1.8. This supplies some indirect support for efficacy of azelastine. Azelastine-treated patients used slightly more antimicrobials than placebo-treated patients. This may be a result of sinusitis and otitis media which occurred more commonly in azelastine-treated patients. These adverse events are discussed in Section 8.8.4.7.b. of this review. Otherwise, the types of medications used were similar in azelastine and placebo groups, and were not likely to affect the efficacy analysis [Volume 44.1, pages 08.67, 08.93-08.100].

Table 8.1.8. Use of concomitant medications [Volume 44.1, pages 08.67, 08.93-08.100].

Concomitant medication	Azelastine N = 113	Placebo N = 110	Total N = 223
Antihistamines, decongestants, nasal corticosteroids, or antihistamine or decongestant combinations	4	9	13
Antimicrobials	8	4	12
All concomitant medications	195	212	407

8.1.4.6. Efficacy endpoint outcomes

Efficacy of azelastine nasal spray, 137 mcg, in the treatment of the symptoms of vasomotor rhinitis was supported by primary and secondary endpoints as described below. Loss of blinding decreases the strength of conclusions drawn from efficacy outcomes in this study. Review of individual primary and secondary efficacy variables are found in the following sections.

8.1.4.6.a. Primary efficacy endpoint

The primary efficacy endpoint was the difference between the TVRSS for the one-week Baseline period and the average of the TVRSSs for the three one-week evaluation periods. This was termed the "Overall" endpoint. Azelastine-treated patients had a statistically superior improvement in the TVRSS from baseline compared with the placebo group for the Overall evaluation period. The protocol specified that the primary analysis was to be the intent-to-treat analysis based on all subjects with any response data. The data presented show different values for N and Mean Baseline TVRSS, indicating that a true intent-to-treat analysis was not used, in contrast to the protocol. The difference between values for N and Mean Baseline TVRSS were small, however, and as a result were not likely to affect conclusions drawn from these data. Results of the primary efficacy endpoint and other efficacy measures are displayed in Table 8.1.9. [Volume 44.1, pages 08.64, 08.104]. Azelastine-treated patients showed statistically superior improvements in the TVRSS from baseline for the Week 1 and Week 2 evaluation periods compared with placebo. Azelastine-treated patients had a numerical, but not statistical, improvement in TVRSS from baseline for the Week 3 evaluation period compared with placebo. Improvement in the placebo group for the for the Week 3 evaluation period resulted in the lack of a statistically significant difference between treatment groups. This improvement in the placebo group could be due to the placebo effect or from regression to the mean. An absolute effect size of 12.8% was observed for the Overall endpoint. The effect size was calculated in the following manner:

Effect size = (Mean TVRSS for evaluation period, placebo - Mean TVRSS for evaluation period, azelastine) x 100
Mean TVRSS for evaluation period, placebo

Table 8.1.9. Improvement from baseline in Total Vasomotor Rhinitis Symptom Scores (TVRSS) [Volume 44.1, pages 08.64, 08.85].

Evaluation period	Treatment group	N[2]	Mean Baseline TVRSS[2]	Mean TVRSS for evaluation period	Mean Improvement in TVRSS	SD[3]	p-value[4]
Overall[1]	**Azelastine**	**111**	**6.51**	**4.97**	**1.54**	**1.47**	**0.002**
	Placebo	**107**	**6.54**	**5.70**	**0.84**	**1.76**	
Week 1	Azelastine	111	6.51	5.38	1.13	1.47	<0.001
	Placebo	107	6.54	6.28	0.26	1.66	
Week 2	Azelastine	108	6.48	4.83	1.65	1.66	0.029
	Placebo	101	6.58	5.44	1.14	1.91	
Week 3	Azelastine	106	6.49	4.57	1.92	1.96	0.120
	Placebo	99	6.53	5.12	1.41	2.19	

[1]Primary efficacy endpoint in bold type.
[2]Different values for N and Mean Baseline TVRSS indicate that an intent-to-treat analysis was not used. Please see text.
[3]Calculated from SD = SE X (Sq Rt of N)
[4]ANOVA

8.1.4.6.b. Secondary efficacy variables

Secondary efficacy variables included reduction in individual symptom scores, percentage of study dropouts, and patient global assessment of therapeutic effectiveness. Individual symptom scores were evaluated in terms of reduction from baseline at each of the three evaluation periods, and Overall, as with the primary efficacy endpoint (see Section 8.1.3.5.a. Primary efficacy variables) [Volume 44.1, page 08.152].

Azelastine-treated patients had a greater degree of improvement in symptom scores than placebo-treated patients of the overall evaluation for rhinorrhea, sneezes, nasal congestion, and postnasal drip. These data are displayed in Table 8.1.10. Improvement in rhinorrhea may be a result of anticholinergic activity of this first generation antihistamine The mechanism of improvement in sneezes is unclear, but may be a result of mild local anesthetic activity. Other first generation antihistamines, such as diphenhydramine, have local anesthetic activity when used topically.

Table 8.1.10. Overall improvement from baseline in individual symptom scores [Volume 44.1, pages 08.87-08.90].

Symptom	Treatment group	N	Mean baseline symptom score	Mean symptom score for evaluation period	Mean Improvement in TVRSS	SD[1]	Effect size[2], %
Rhinorrhea	Azelastine	111	1.49	1.01	0.48	0.53	13
	Placebo	107	1.58	1.27	0.31	0.62	
Sneezes	Azelastine	111	0.85	0.60	0.25	0.42	22
	Placebo	107	0.85	0.77	0.08	0.41	
Nasal congestion	Azelastine	111	2.11	1.75	0.36	0.42	5
	Placebo	107	2.04	1.85	0.19	0.52	
Postnasal drip	Azelastine	111	2.07	1.63	0.44	0.53	10
	Placebo	107	2.08	1.82	0.26	0.62	

[1]Calculated from SD = SE X (Sq Rt of N)
[2]Effect size = (Mean symptom score for evaluation period, placebo - Mean symptom score for evaluation period, azelastine) x 100
Mean symptom score for evaluation period, placebo

Improvements in rhinorrhea, sneezes, nasal congestion, and postnasal drip were also seen for the each of the three treatment periods, Week 1, Week 2, and Week 3. The difference between azelastine group and the placebo group was less pronounced at Week 2 than at Week 1 and at Week 3 than at Week 2. This is a result of improvement in the placebo group. As with the primary efficacy variable, data presented show different values for N and mean baseline symptom scores indicating that a true intent-to-treat analysis was not used. The difference between values for N and baseline symptom scores were small, however, and as a result were not likely to affect conclusions drawn from these data. These data are displayed in Table 8.1.11.

Table 8.1.11. Improvement from baseline in individual symptom scores, Weeks 1, 2, and 3 [Volume 44.1, pages 08.87-08.90].

Symptom	Evaluation period	Treatment group	N[1]	Mean baseline symptom score[1]	Mean symptom score for evaluation period	Mean improvement in symptom score	SD[2]
Rhinorrhea	Week 1	Azelastine	111	1.49	1.12	0.37	0.53
		Placebo	107	1.58	1.46	0.12	0.62
	Week 2	Azelastine	108	1.49	0.98	0.51	0.62
		Placebo	101	1.51	1.10	0.41	0.70
	Week 3	Azelastine	106	1.49	0.91	0.58	0.62
		Placebo	99	1.58	1.11	0.47	0.70
Sneezes	Week 1	Azelastine	111	0.85	0.64	0.21	0.42
		Placebo	107	0.85	0.85	0.00	0.52
	Week 2	Azelastine	108	0.85	0.56	0.29	0.52
		Placebo	101	0.87	0.75	0.12	0.50
	Week 3	Azelastine	106	0.84	0.55	0.29	0.51
		Placebo	99	0.85	0.68	0.17	0.50
Nasal congestion	Week 1	Azelastine	111	2.11	1.86	0.25	0.53
		Placebo	107	2.04	1.97	0.07	0.52
	Week 2	Azelastine	108	2.09	1.69	0.40	0.52
		Placebo	101	2.03	1.76	0.27	0.60
	Week 3	Azelastine	106	2.09	1.64	0.45	0.62
		Placebo	99	2.04	1.72	0.32	0.70
Postnasal drip	Week 1	Azelastine	111	2.07	1.77	0.30	0.53
		Placebo	107	2.08	2.00	0.08	0.62
	Week 2	Azelastine	108	2.06	1.62	0.44	0.62
		Placebo	101	2.09	1.74	0.35	0.70
	Week 3	Azelastine	106	2.07	2.01	0.61	0.62
		Placebo	99	2.07	1.99	0.45	0.80

[1]Different values for N and mean baseline symptom scores indicate that an intent-to-treat analysis was not used. Please see text.
[2]Calculated from SD = SE X (Sq Rt of N)

There were more dropouts in placebo-treated patients than azelastine-treated patients for each evaluation period and overall. These data are displayed in Table 8.1.12.

Table 8.1.12. Dropouts during double-blind treatment [Volume 44.1, pages 08.91].

Period	Treatment group	N	Dropouts	
			n	(%)
Week 1	Azelastine	113	4	(4)
	Placebo	110	7	(6)
Week 2	Azelastine	109	1	(1)
	Placebo	103	3	(3)
Week 3	Azelastine	108	2	(2)
	Placebo	100	3	(3)
Overall	Azelastine	113	7	(6)
	Placebo	110	13	(12)

There was little difference between azelastine and placebo in the patients global assessment of therapeutic effectiveness. A small majority of both azelastine-treated patients and placebo-treated patients indicated they would continue their medication if it was commercially available, and the proportion of patients that would choose to continue their study medication was similar in both treatment groups. These data are displayed in Table 8.1.13. The lack of difference between azelastine and placebo in patient global assessment of effectiveness is perplexing in light of the efficacy demonstrated in the primary and other secondary efficacy endpoints. This discrepancy could be a result of a factor such as poor taste of the vehicle that would incline patients not to use the drug despite a clinical response.

Table 8.1.13. Patient global assessment of therapeutic effectiveness [Volume 44.1, pages 08.92].

Treatment group	N	Yes		No	
		n	(%)	n	(%)
Azelastine	111	60	(54)	51	(46)
Placebo	104	59	(57)	45	(43)

8.1.4.7. Safety outcomes

Safety variables included AEs, VS, PE, CBC, chemistry, and urinalysis. ECGs were not performed [Volume 44.1, pages 08-151-08.152]. Each variable is discussed below. This study supports the safety of azelastine nasal spray, 137 mcg in the treatment of the symptoms of vasomotor rhinitis.

Drug exposure was adequate to assess safety. Adverse events (AEs) were slightly less frequent in azelastine-treated patients than in placebo-treated patients. AEs occurring more frequently in azelastine-treated patients than in placebo-treated patients included taste perversion, dysesthesia, pharyngitis, rhinitis, sinusitis, somnolence, and diarrhea. There were no deaths or serious adverse events in this study. Eight patients in the azelastine group had elevated AST (SGOT) and/or ALT (SGPT) levels at the close of the study. There were no patients in the placebo group that developed elevated AST and/or ALT levels.

8.1.4.7.a. Total drug exposure

Total drug exposure may be estimated from compliance data. Compliance was determined by review of patient diary entries. These data are reviewed in Section 8.1.4.4., Compliance, and displayed in Table 8.1.7. Patients were to record the time for each dose of study medication that was taken. Only 8.9% of azelastine-treated patients and 13.6% of placebo-treated patients received less than 20 days of the 21-day course of study medication. In the azelastine group, 77.9% of patients were treated for 20 to 22 days, and in the placebo group, 70.0% of