patients were treated for 20 to 22 days [Volume 44.1, pages 08.68, 08.104]. In this reviewer's opinion, drug exposure was adequate to assess safety.

8.1.4.7.b. Adverse events (AEs)

Adverse events (AEs) were slightly less frequent in azelastine-treated patients than in placebo-treated patients, with 53 patients in the azelastine group (47%, 53/113) and 58 patients in the placebo group (53%, 58/110) that reported AEs [Volume 44.1, pages 08.68-08.69, 08.106-08.107]. Taste perversion was the most common AE occurring more frequently in azelastine-treated patients (15%, 17/113) than in placebo-treated patients (4%, 4/110). Other AEs occurring more frequently in azelastine-treated patients than in placebo-treated patients included dysesthesia, pharyngitis, rhinitis, sinusitis, somnolence, and diarrhea. These data are displayed in Table 8.1.14. Taste perversion, dysesthesia, and rhinitis were the most common AEs the investigator considered to have a probable or definite relation to study medication. [Volume 44.1, pages 08.69, 08.108].

It is interesting to note that sinusitis was more common in azelastine-treated patients than in placebo-treated patients. In addition, there was one patient in the azelastine group and none in the placebo group that developed otitis media. These AEs are the likely explanation for the higher frequency of concomitant antimicrobial use noted earlier in this review. This observation also raises the question that azelastine might predispose to the development of bacterial upper respiratory infection. Possible causes might be irritation to the mucosal barrier, thickening of mucus, and/or interference with normal mucociliary function. Future AEs reports should be monitored for additional instances of bacterial upper respiratory infection. Bitter taste, somnolence, pharyngitis, and rhinitis are noted in current azelastine product information.

Table 8.1.14. Adverse events occurring more commonly in azelastine-treated patients at a rate ≥2% [Volume 44.1, pages 08.106-08.108].

Adverse event	Azelastine N = 113		Placebo N = 110		Total N = 223	
	n	(%)	n	(%)	n	(%)
Taste perversion	17	(15)	4	(4)	21	(9)
Dysesthesia	11	(10)	4	(4)	15	(7)
Pharyngitis	10	(9)	8	(7)	18	(8)
Rhinitis	8	(7)	3	(3)	11	(5)
Sinusitis	5	(4)	1	(1)	6	(3)
Somnolence	2	(2)	0	(0)	2	(1)
Diarrhea	2	(2)	0	(0)	2	(1)
All adverse events	93	(82)	88	(80)	181	(81)
All patients with an adverse event	53	(47)	58	(53)	111	(50)

8.1.4.7.c. Deaths and serious adverse events (SAEs)

There were no deaths or serious adverse events in this study [Volume 44.1, page 08.6].

8.1.4.7.d. Withdrawals due to AEs

One azelastine-treated patient (#161) withdrew because of conjunctivitis and taste perversion. Three placebo-treated patients withdrew because of AEs, one each for rash (#161), influenza-like symptoms (#103), and nausea (#306) [Volume 44.1, pages 08.68, 08.105, Volume 44.26, pages 12.1-12.104].

8.1.4.7.e. Vital signs

There were no clinically significant changes in vital signs or body weight in patients in either azelastine or placebo groups [Volume 44.1, pages 08.68, 08.103].

8.1.4.7.f. Physical Examination

There were small numbers of changes in physical examination considered by the investigator to be clinically significant. These data are presented in Table 8.1.15. The types and frequency of physical exam abnormalities were similar in azelastine- and placebo-treated groups. Review of these data reveals that these abnormalities were mild and included nasal mucosal edema, pharyngitis, mucus discharge, cervical adenopathy, and wheeze with increased expiratory phase [Volume 44.1, pages 08.67, 08.102, Volume 44.14, pages 11.414-11.635].

Table 8.1.15. Clinically significant physical examination changes, Study 335 [Volume 44.1, page 80.102].

Category	Azelastine N = 113		Placebo N = 110	
Nose	5	(4)	3	(3)
Mouth/Throat	2	(2)	1	(1)
Lymph nodes	1	(1)	0	(0)
Lungs/Thorax	0	(0)	1	(1)

8.1.4.7.g. Laboratory studies

Eight patients in the azelastine group developed elevated AST (SGOT) and/or ALT (SGPT) levels at the close of the study, Visit 4. A listing of these patients is presented in Table 8.1.16. There were no patients in the placebo group that developed elevated AST and/or ALT levels. One azelastine-treated patient, #53 at Study Center 980006, had an AST of 186 IU/mL and ALT of 735 IU/mL at Visit 4. AST and ALT levels for this patient were normal at baseline. AST and ALT fell to 30 and 71 IU/mL, respectively, ten days later in this patient who continued to use azelastine after the end of the study [Volume 44.1, pages 08.69-08.71]. Other patients had mild elevations in AST and/or ALT, with elevations less than twice normal.

Table 8.1.16. Increase in AST (SGOT) and ALT (SGPT) in azelastine-treated patients, Study 335 [Volume 44.1, pages 08.69-08.71; Volume 44.15, pages 11.755-11.756, 11.759-11.761, 11.902-11.903, 11.1192-1194].

Study Center	Patient	AST, IU/mL			ALT, IU/L		
		Baseline	Visit 4	Follow-up	Baseline	Visit 4	Follow-up
980006	53	21	186	30	16	735	71
980017	262	19	168	59	18	67	67
980011	155	20	37	ND	8	33	ND
980013	185	31	45	ND	24	53	ND
980014	204	24	33	ND	41	55	ND
980014	208	16	32	ND	17	41	ND
980017	268	24	37	ND	29	40	ND
980018	285	22	31	ND	37	57	ND

Laboratory normal ranges: AST Males 11-36 IU/mL, Females 6-34 IU/mL ALT Males 6-43 IU/mL, Females 6-43 IU/mL [Volume 44.15, page 11.728]

A slightly higher rate of elevated AST and/or ALT was noted in figures in Dr. Himmel's original NDA review of azelastine [Medical Officer review, NDA 20-114, 7/19/93, pages 70-71]. In addition, his review notes that preclinical data showed elevated levels of AST, ALT, reversible fatty changes in the liver, and hepatocellular hypertrophy at doses of 30 mg/kg/day [Medical Officer review, NDA 20-114, 7/19/93, page 6].

Infrequent occurrences of hepatic transaminase elevations are noted in the current product labeling for Astelin® Nasal Spray.

There was a slightly higher rate of elevated MCV in azelastine-treated patients (13%, 13/104) than in placebo-treated patients (7%, 7/96). Mean MCV levels increased in both treatment groups a similar amount with a mean increase of 1.42 fL in the azelastine group and 0.99 fL in the placebo group. There was no significant changes in the mean hemoglobin and hematocrit in either treatment group. [Volume 44.1, pages 08.109, 08.117]. This is not likely to represent a new safety signal.

There was a slightly higher rate of elevated triglycerides in azelastine-treated patients (14%, 13/95) than in placebo-treated patients (8%, 7/83). Mean triglyceride levels increased in both treatment groups a similar amount with a mean increase of 15.70 mg/dL in the azelastine group and 18.98 mg/dL in the placebo group, however [Volume 44.1, pages 08.111, 08.121]. This is not likely to represent a new safety signal.

8.2. Study 336: 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: 6/2/99
Study report dated: 11/2/99

8.2.1. 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 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.

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 203 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 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.

There was adequate exposure to study drug to assess safety. Adverse events (AEs) were more 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, somnolence, rhinitis, epistaxis, back pain, urinary tract infection, paresthesia, dry mouth, and thirst. Bitter taste, somnolence, pharyngitis, rhinitis, dry mouth, and epistaxis 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. This study supports the safety of azelastine nasal spray.

8.2.2. 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 44.4, page 08.946].

8.2.3. 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. Study design, baseline evaluation, and randomization were the same as Study 335, reviewed in Section 8.2.3. of this review. [Volume 44.4, pages 08.949-08.960].

The severity of vasomotor rhinitis symptoms was assessed using the same four-point scales used in Study 335, and are presented in Table 8.8.1 [Volume 44.4, pates 08.957-08.958].

As in Study 335, the benefit of blinding may have been lost because of the taste of azelastine, and this loss of blinding decreases the confidence of conclusions from efficacy outcomes.

Patients were to monitor their vasomotor rhinitis symptoms twice a day during the three-week treatment period in the same fashion as Study 335 using the scales displayed in Table 8.1.1. Patients scored their symptoms for the same four treatment periods as Study 335: 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 44.4, pages 08.955, 08.958-08.959].

8.2.3.1. Inclusion criteria [Volume 44.4, pages 08.950-08.951]

Patients were to meet the same following inclusion criteria as in Study 335. These are displayed in Section 8.1.3.1. of this review.

8.2.3.2. Exclusion criteria [Volume 44.4, pages 08.951-952]

Patients were not to be enrolled into the study if they had any of the exclusion criteria in Study 335. These are displayed in Section 8.1.3.2. of this review.

As in Study 335, inclusion and exclusion criteria pertaining to use of contraceptives was amended on February 8, 1999 to allow use of oral, implant, or injectable contraceptives [Volume 44.4, page 08.1062-08.1064]. These changes are discussed in Section 8.1.3.2. of this review.

8.2.3.3. Drug product and placebo [Volume 44.4, page 08.953]

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 were the same as in Study 335:

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.].

8.2.3.4. Assessment of signs and symptoms

As with Study 335, 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 8.1.2. Assessment was based on the severity of symptoms over the preceding one-half day (reflective). A total vasomotor rhinitis symptom score (TVRSS) was calculated for each one week evaluation period, Baseline through Week 3, making up the three-week treatment period [Volume 44.4, pages 08.958–08.959].

8.2.3.5. Variables

Efficacy and safety variables for this study were the same as those of Study 335, and are outlined below.

8.2.3.5.a. Primary efficacy variable

The primary efficacy variable was the Total Vasomotor Rhinitis Symptom Score (TVRSS). As with Study 335, the primary efficacy endpoint was 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 44.4, page 08.1047-08.1048].

The primary efficacy endpoint was calculated in the same manner as in Study 335, and is described in Section 8.1.3.5.a. of this review [Volume 44.4, pages 08.962-08.963, 08.1043-08.1044, 08.1047-80.1048].

8.2.3.5.b. Secondary efficacy variables

Secondary efficacy variables were the same as in Study 335 and are described in Section 8.1.3.5.b. of this review [Volume 44.4, pages 08.1043-1044].

8.2.3.5.c. Safety variables

Safety variables were the same as in Study 335 and included AEs, VS, PE, CBC, chemistry, and urinalysis. ECGs were not performed [Volume 44.4, pages 08151-08.152].

8.2.3.6. Statistical Considerations

Statistical analysis of efficacy outcomes were the same as in Study 335, and are described in Section 8.1.3.6 of this review [Volume 44.4, pages 08.961-08.962, 08.1044-08.1050].

As with Study 335, approximately 80 patients per treatment group were required to detect a 10 point difference between treatment groups in reduction of symptom scores. Power analysis is discussed in Section 8.1.3.6 of this review [Volume 44.4, page 08.1050].

8.2.4. Results

8.2.4.1. Populations enrolled/analyzed

There were 331 patients screened for participation in this study. Of these 331 patients screened, 128 were not randomized. Reasons for patients failing to qualify for randomization included low symptom scores (33%, 42/128), positive nasal smear for eosinophils (23%, 29/128), abnormal sinus X-ray (11%, 14/128), administrative reasons such as loss to follow-up or withdrawal of consent (10%, 13/128), and positive allergen skin test (9%, 12/128) [Volume 44.4, pages 08.964, 08.976].

There were 203 patients randomized to study treatment with 103 in the azelastine group and 100 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 significance of outcome differences between study groups is likely to be inflated.

Of the 203 patients randomized, 22 did not complete the study, with 14 in the azelastine group and eight in the placebo group. Reasons for noncompletion of the study are listed in Table 8.2.1. The most common reasons for noncompletion were protocol violation and treatment failure. The majority of protocol violations were for incorrect randomization because of pre-existing significant medical conditions or use of prohibited medications [Volume 44.4, pages 08.981, 08.979, Volume 44.24, pages 11.4515-11.4522]. Protocol violations are displayed in Table 8.2.2. The small number of protocol violations are not likely to influence efficacy and safety conclusions from this study.

There were seven patients excluded from the intent-to-treat analysis because of the lack of data other than the baseline visit. These patients included six randomized to azelastine and one randomized to placebo [Volume 44.4, pages 08.965, 08.980].

Table 8.2.1. Patient disposition [Volume 44.4, pages 08.964, 08.975-08.978].

	Azelastine		Placebo		All patients	
	N	(%)	N	(%)	N	(%)
Number of patients randomized	103	(100)	100	(100)	203	(100)
Number of patients completing study	89	(86.4)	92	(92.0)	181	(89.1)
Number of patients discontinued	14	(13.6)	8	(8.0)	22	(10.8)
Adverse event	4	(3.9)	2	(2.0)	6	(3.0)
Intercurrent illness	1	(1.0)	1	(1.0)	2	(1.0)
Loss to follow-up	2	(1.9)	1	(1.0)	3	(1.5)
Administrative	2	(1.9)	0	(0)	2	(1.0)
Protocol violation	5	(4.9)	3	(3.0)	8	(3.9)
Treatment failure	0	(0)	1	(1.0)	1	(0.5)

Table 8.2.2. Protocol violations [Volume 44.4, pages 08.981, 08.979, Volume 44.24, pages 11.4515-11.4522].

Center	Treatment	Subject number	Protocol violation
980031	Azelastine	153	Disallowed cardiac medication
980032	Azelastine	162	Significant pre-existing medical condition, hypothyroidism
980033	Azelastine	181	Improper symptom scoring
980033	Azelastine	185	Significant pre-existing medical condition, hypothyroidism
980037	Azelastine	270	Noncompliance
980024	Placebo	3	Disallowed medication
980031	Placebo	147	Significant pre-existing medical condition, hypothyroidism
980033	Placebo	186	Significant pre-existing medical condition, hypothyroidism

8.2.4.2. Baseline demographic and background characteristics

Demographics are presented in Table 8.2.3. The population studied was largely Caucasian. There were more females than males in the study. The mean age was approximately 41 years in both treatment groups. There were small numbers of patients ages 12-15 years in both treatment groups. There were two patients > 65 years in the study, Patients #262 and #263. These patients were not listed as protocol violators, as they should have been. It is unlikely, however, that these two patients would have affected the efficacy analysis. Both treatment groups had similar age distributions. Treatment groups were similar in gender and race [Volume 44.4, pages 08.965, 08.982, Volume 44.20, pages 11.2529-11.2534].

Table 8.2.3. Study 336, demographics [Volume 44.4, page 08.982, Volume 44.20, pages 11.2529-11.2534]

Characteristic	Azelastine N = 103		Placebo N = 100		Total N = 203	
Age, years	n	(%)	n	(%)	n	(%)
12-15	4	(4)	3	(3)	7	(3)
16-19	6	(6)	3	(3)	9	(4)
20-29	11	(11)	16	(16)	27	(13)
30-39	19	(18)	20	(20)	39	(19)
40-49	33	(32)	31	(31)	64	(32)
50-59	24	(23)	20	(20)	44	(22)
60-65	5	(5)	6	(6)	11	(5)
>65	1	(1)	1	(1)	2	(1)
Mean age	41.5		40.7		41.1	
SD	13.0		13.0		13.0	

Characteristic	Azelastine N = 103		Placebo N = 100		Total N = 203	
Gender	n	(%)	n	(%)	n	(%)
Male	17	(17)	27	(27)	44	(22)
Female	86	(83)	73	(73)	159	(78)
Race	n	(%)	n	(%)	n	(%)
Caucasian	92	(91)	90	(90)	182	(90)
Black	5	(5)	4	(4)	9	(4)
Other	4	(4)	6	(6)	10	(5)

8.2.4.3. Protocol deviations

There were 38 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 16 in the azelastine group and 13 in the placebo group. There were seven protocol deviations in the azelastine group and five in the placebo group for use of antihistamines, decongestants, or sympathomimetics [Volume 44.4, pages 08.981].

8.2.4.4. Compliance

Compliance was determined by review of patient diary entries. These data are displayed 8.2.4. Patients were to record the time for each dose of study medication that was taken. In the azelastine group, 14.6% of patients received less than 20 days of the 21-day course of study medication, but in the placebo group, 7.0% of patients received less than 20 days of the 21-day course of study medication. In the azelastine group, 73.8% of patients were treated for 20 to 22 days, and in the placebo group, 82.0% of patients were treated for 20 to 22 days. The duration of treatment was 23 to 29 days in 11.6% of the azelastine group and 10.0% of the placebo group. Treatment for more than the specified duration was a result of scheduling delays for follow-up visits [Volume 44.4, pages 08.970, 08.1004]. In this reviewer's opinion, compliance was adequate to assess efficacy and safety.

Table 8.2.4. Patient compliance [Volume 44.4, page 08.1004].

Duration of treatment	Azelastine n	(%)	Placebo n	(%)	Total n	(%)
0 to 19 days	15	(14.6)	7	(7.0)	22	(10.8)
20 days	12	(11.6)	5	(5.0)	17	(8.4)
21 days	33	(32.0)	43	(43.0)	76	(37.4)
22 days	31	(30.0)	34	(34.0)	65	(32.0)
23 to 29 days	12	(11.6)	10	(10.0)	22	(10.8)
Total	103	(100)	100	(100)	203	(100)

8.2.4.5. Use of concomitant medications

The use of concomitant medications was similar in the azelastine and placebo groups. Azelastine-treated patients used slightly more antihistamines, decongestants, nasal corticosteroids, or antihistamine/decongestant combinations than placebo-treated patients. These data are displayed in Table 8.2.5. Azelastine-treated and placebo-treated patients used similar amounts of antimicrobials. Otherwise, the types of medications used were similar in azelastine and placebo groups, and were not likely to affect the efficacy analysis [Volume 44.4, pages 08.969, 08.994-08.1000].

Table 8.2.5. Use of concomitant medications [Volume 44.4, pages 08.969, 08.994-08.1000].

Concomitant medication	Azelastine N = 103	Placebo N = 100	Total N = 203
Antihistamines, decongestants, nasal corticosteroids, or antihistamine or decongestant combinations	6	3	9
Antimicrobials	7	8	15
All concomitant medications	196	177	373

8.2.4.6. 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 decrease the strength of conclusions drawn from efficacy outcomes in this study.

8.2.4.6.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. 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 8.2.6. [Volume 44.4, pages 08.966, 08.986]. 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. Azelastine-treated patients showed statistically superior improvements in the TVRSS from baseline for the Week 1, Week 2, and Week 3 evaluation periods compared with placebo. An absolute effect size of 13.6% was observed for the Overall endpoint. The effect size was calculated in the following manner:

$$\text{Effect size} = \frac{(\text{Mean TVRSS for evaluation period, placebo} - \text{Mean TVRSS for evaluation period, azelastine}) \times 100}{\text{Mean TVRSS for evaluation period, placebo}}$$

Table 8.2.6. Improvement from baseline in Total Vasomotor Rhinitis Symptom Scores (TVRSS) [Volume 44.4, pages 08.966, 08.986].

Evaluation period	Treatment group	N[2]	Baseline TVRSS[2]	Mean TVRSS for evaluation period	Mean Improvement in TVRSS	SD[3]	p-value[4]
Overall[1]	Azelastine	97	6.52	4.98	1.54	1.77	0.005
	Placebo	99	6.65	5.77	0.88	1.79	
Week 1	Azelastine	97	6.52	5.42	1.10	1.77	0.042
	Placebo	99	6.65	6.03	0.62	1.59	
Week 2	Azelastine	91	6.56	4.84	1.72	2.00	0.005
	Placebo	95	6.62	5.70	0.92	2.05	
Week 3	Azelastine	91	6.56	4.63	1.93	2.10	0.006
	Placebo	94	6.65	5.61	1.04	2.13	

[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

8.2.4.6.b. Secondary efficacy variables

Secondary efficacy variables included reduction in individual symptom scores, percentage of study dropouts, and patient global assessment of therapeutic effectiveness. As in Study 335,

individual symptom scores were evaluated in terms of reduction from baseline at each of the three evaluation periods, and Overall (see Section 8.1.3.5.a. Primary efficacy variables) [Volume 44.4, page 08.1049].

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 [Volume 44.4, pages 08.988-08.991]. These data are displayed in Table 8.2.7. Improvement in rhinorrhea may be a result of anticholinergic activity of this first-generation antihistamine. The mechanism of action for sneezing is unclear, but may be a result of mild local anesthetic activity. Other antihistamines, such as diphenhydramine, have a local anesthetic activity when used topically.

Table 8.2.7. Overall improvement from baseline in individual symptom scores [Volume 44.4, pages 08.988-08.991].

Symptom	Treatment group	N[1]	Baseline symptom score[1]	Mean symptom score for evaluation period	Mean improvement in TVRSS	SD[2]	Effect size[3], %
Rhinorrhea	Azelastine	97	1.52	1.04	0.48	0.69	23
	Placebo	99	1.61	1.35	0.26	0.60	
Sneezes	Azelastine	97	0.82	0.61	0.21	0.49	22
	Placebo	99	0.91	0.78	0.13	0.50	
Nasal congestion	Azelastine	97	2.08	1.71	0.37	0.49	6
	Placebo	99	2.05	1.81	0.24	0.60	
Postnasal drip	Azelastine	97	2.10	1.62	0.48	0.69	11
	Placebo	99	2.08	1.82	0.26	0.60	

[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)
[3]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. [Volume 44.4, pages 08.988-08.991]. 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 8.2.8.

Table 8.2.8. Improvement from baseline in individual symptom scores, Weeks 1, 2, and 3 [Volume 44.1, pages 08.988-08.991].

Symptom	Evaluation period	Treatment group	N	Baseline symptom score	Mean symptom score for evaluation period	Mean improvement in symptom score	SD*
Rhinorrhea	Week 1	Azelastine	97	1.52	1.16	0.36	0.59
		Placebo	99	1.61	1.44	0.17	0.60
	Week 2	Azelastine	91	1.53	1.00	0.53	0.76
		Placebo	95	1.61	1.33	0.28	0.68
	Week 3	Azelastine	91	1.53	0.93	0.60	0.76
		Placebo	94	1.61	1.31	0.30	0.78

Symptom	Evaluation period	Treatment group	N	Baseline symptom score	Mean symptom score for evaluation period	Mean improvement in symptom score	SD*
Sneezes	Week 1	Azelastine	97	0.82	0.69	0.13	0.59
		Placebo	99	0.91	0.77	0.14	0.50
	Week 2	Azelastine	91	0.85	0.61	0.24	0.57
		Placebo	95	0.89	0.79	0.10	0.58
	Week 3	Azelastine	91	0.85	0.60	0.25	0.57
		Placebo	94	0.90	0.79	0.11	0.58
Nasal congestion	Week 1	Azelastine	97	2.08	1.82	0.26	0.59
		Placebo	99	2.05	1.87	0.18	0.60
	Week 2	Azelastine	91	2.10	1.69	0.41	0.57
		Placebo	95	2.04	1.81	0.23	0.68
	Week 3	Azelastine	91	2.10	1.61	0.49	0.67
		Placebo	94	2.05	1.76	0.29	0.68
Postnasal drip	Week 1	Azelastine	97	2.10	1.75	0.35	0.69
		Placebo	99	2.08	1.94	0.14	0.50
	Week 2	Azelastine	91	2.08	1.54	0.54	0.76
		Placebo	95	2.08	1.77	0.31	0.68
	Week 3	Azelastine	91	2.08	1.49	0.59	0.86
		Placebo	94	2.09	1.76	0.33	0.68

*Calculated from SD = SE X (Sq Rt of N)

There were more dropouts in azelastine-treated patients than placebo-treated patients for each evaluation period and overall [Volume 44.4, pages 08.992]. These data are displayed in Table 8.2.9.

Table 8.2.9. Dropouts during double-blind treatment [Volume 44.4, pages 08.992].

Period	Treatment group	N	Dropouts n	(%)
Week 1	Azelastine	103	10	(10)
	Placebo	100	4	(4)
Week 2	Azelastine	93	1	(1)
	Placebo	96	2	(2)
Week 3	Azelastine	92	3	(3)
	Placebo	94	2	(2)
Overall	Azelastine	103	14	(14)
	Placebo	100	8	(8)

A higher percentage of azelastine-treated patients than placebo-treated patients indicated that they would continue their medication if it was commercially available. This provides some support of the efficacy of azelastine. These data are displayed in Table 8.2.10.

Table 8.2.10. Patient global assessment of therapeutic effectiveness [Volume 44.4, pages 08.933].

Treatment group	N	Yes n	(%)	No n	(%)
Azelastine	97	50	(52)	47	(48)
Placebo	98	35	(36)	63	(64)

8.2.4.7. 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 more 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, somnolence, rhinitis, epistaxis, back pain, urinary tract infection, paresthesia, dry mouth, and thirst. There were no deaths or serious adverse events in this study.

8.2.4.7.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 displayed 8.2.4. Patients were to record the time each dose of study medication was taken. In the azelastine group, 14.6% of patients received less than 20 days of the 21-day course of study medication, but in the placebo group, 7.0% of patients received less than 20 days of the 21-day course of study medication. In the azelastine group, 73.8% of patients were treated for 20 to 22 days, and in the placebo group, 82.0% of patients were treated for 20 to 22 days [Volume 44.4, pages 08.970, 08.1004]. In this reviewer's opinion, compliance was adequate to assess safety.

8.2.4.7.b. Adverse events (AEs)

Adverse events (AEs) were more frequent in azelastine-treated patients than in placebo-treated patients, with 56 patients in the azelastine group (54%, 54/103) and 33 patients in the placebo group (33%, 33/100) that reported AEs [Volume 44.4, pages 08.970-08.971, 08.1006-08.1007]. Taste perversion was the most common AE occurring more frequently in azelastine-treated patients (24%, 25/103) than in placebo-treated patients (1%, 1/100). Other AEs occurring more frequently in azelastine-treated patients than in placebo-treated patients included dysesthesia, somnolence, rhinitis, epistaxis, back pain, urinary tract infection, paresthesia, dry mouth, and thirst. These data are displayed in Table 8.2.11.

Bitter taste, somnolence, pharyngitis, rhinitis, dry mouth, and epistaxis are noted in current azelastine product information. Taste perversion, and dysesthesia were the most common AEs the investigator considered to have a probable or definite relation to study medication. [Volume 44.4, pages 08.971, 08.1008]

Table 8.2.11. Adverse events occurring more commonly in azelastine-treated patients at a rate ≥2% [Volume 44.4, pages 08.1006-08.1007].

Adverse event	Azelastine N = 103		Placebo N = 100		Total N = 203	
	n	(%)	n	(%)	n	(%)
Taste perversion	25	(24)	1	(1)	26	(13)
Dysesthesia	6	(6)	3	(3)	9	(4)
Somnolence	5	(5)	2	(2)	7	(3)
Rhinitis	4	(4)	2	(2)	6	(3)
Epistaxis	4	(4)	0	(0)	4	(2)
Back pain	3	(3)	1	(1)	4	(2)
Urinary tract infection	3	(3)	0	(0)	3	(1)
Paresthesia	2	(2)	0	(0)	2	(1)
Mouth dry	2	(2)	0	(0)	2	(1)
Thirst	2	(2)	0	(0)	2	(1)
All adverse events	92	(89)	54	(54)	146	(72)
All patients with an adverse event	56	(54)	33	(33)	89	(44)

8.2.4.7.c. Deaths and serious adverse events (SAEs)

There were no deaths or serious adverse events in this study [Volume 44.1, page 08.6].

8.2.4.7.d. Withdrawals due to AEs

There were five azelastine treated patients and three placebo-treated patients that withdrew from the study because of AEs. Two azelastine-treated patients, (#241 and # 280) withdrew because of somnolence, an AE that is noted in the current product information. There were no withdrawals due to somnolence in placebo-treated patients. Withdrawals due to AEs are presented in Table 8.2.12. [Volume 44.4, pages 08.970, 08.1005, Volume 44.26, pages 12.105-12.308]. Azelastine-treated patient #317 developed back pain and bruising as a result of a fall from a bicycle and required an excluded medication. Bruising was coded as "purpura" in this patient.

Table 8.2.12. Study 336, withdrawals due to AEs (Volume 44.4, page 08.1005, Volume 44.26, pages 12.105-12.308].

Treatment group	Center	Subject	Adverse event(s)
Azelastine	980025	317	Back pain, purpura*
Azelastine	980031	157	Sinusitis
Azelastine	980036	241	Somnolence
Azelastine	980036	248	Accidental injury
Azelastine	980037	280	Somnolence, agitation, peripheral edema
Placebo	980027	66	Urticaria
Placebo	980027	71	Headache, pyorrhea
Placebo	980031	154	Asthma

*Back pain and bruising secondary to fall from bicycle. Bruising from trauma coded as "purpura."

8.2.4.7.e. Vital signs

There were no clinically significant changes in vital signs or body weight in patients in either azelastine or placebo groups [Volume 44.4, pages 08.970, 08.1003].

8.2.4.7.f. Physical Examination

There were small numbers of changes in physical examination considered by the investigator to be clinically significant. These data are presented in Table 8.2.13. Abnormalities of the mouth and throat were seen in six azelastine-treated patients and in one placebo-treated patient. These mouth and throat abnormalities were mild and consisted of pharyngitis, cobblestoning, and postnasal drip. The types and frequency of other physical exam abnormalities were similar in azelastine- and placebo-treated groups. Review of these data reveals that these other abnormalities were also mild and included nasal mucosal edema and erythema, infraorbital puffiness, and middle ear fluid [Volume 44.4, pages 08.969, 08.1002, Volume 44.21, pages 11.2925-11.3127].

Table 8.2.13. Clinically significant physical examination changes, Study 336 [Volume 44.4, page 80.1002].

Category	Azelastine N = 103		Placebo N = 100	
Head	1	(1)	0	(0)
Eyes	0	(0)	1	(1)
Ears	0	(0)	1	(1)
Nose	6	(6)	4	(4)
Mouth/Throat	6	(6)	1	(1)

8.2.4.7.g. Laboratory studies

Four patients each in the azelastine and placebo groups developed elevated AST (SGOT) and/or ALT (SGPT) levels at the close of the study, Visit 4. A listing of these patients is presented in Table 8.2.14. Follow-up samples were not drawn on these patients because the small elevations in AST and ALT were not considered to be clinically significant. Mean changes in ALT and AST from baseline were similar in azelastine- and placebo-treated patients [Volume 44.4, page 08.1018].

Table 8.2.14. Increase in AST (SGOT) and ALT (SGPT) in azelastine-treated patients, Study 336 [Volume 44.1, pages 08.69-08.71, Volume 44.22, pages 11.3254-11.3255, 11.3282-11.3283, 11.3360-11.3361, 11.3385-3387, 11.3462-11.3463, 11.3511-11.35412, 11.3588-11.3589, 11.3615-11.3616].

Treatment	Study Center	Patient	AST, IU/mL		ALT, IU/L	
			Baseline	Visit 4	Baseline	Visit 4
Azelastine	980025	28	24	40	23	28
Azelastine	980028	90	19	69	21	84
Azelastine	980033	192	28	33	40	53
Azelastine	980037	273	34	42	34	38
Placebo	980025	23	24	32	29	50
Placebo	980028	91	19	26	37	52
Placebo	980031	152	24	29	32	51
Placebo	980036	242	27	31	31	42

Laboratory normal ranges: AST Males 11-36 IU/mL, Females 9-34 IU/mL ALT Males 6-43 IU/mL, Females 6-34 IU/mL
[Volume 44.21, page 11.3223]

There was a slightly lower rate of elevated triglycerides in azelastine-treated patients (11%, 8/93) than in placebo-treated patients (15%, 12/93). There was a larger increase in mean triglyceride levels in the placebo group (4.99 mg/dL) than the azelastine group (-0.50 mg/dL) [Volume 44.4, pages 08.1011, 08.1019]. These small changes are not likely to represent a new safety signal.

8.3. Study 337: Studies of the clinical effect of E-0659 [azelastine HCl tablets, 1 mg] on so-called vasomotor rhinitis

8.3.1. Summary and reviewer's conclusion of study results

This was an open label, two-week Japanese study performed in eleven patients with vasomotor rhinitis. The submission includes a translation of the article from the published literature and a copy of the article in the original language. The study was published in Otolaryngology (Japan) 29(4):496-504, 1983. This study used a different dose form, route, and dosage than that proposed in this efficacy supplement. Exposure to drug was not sufficient to assess safety. In addition, this study was small and unblinded, and the data submitted was limited to a translation of the article and a copy of the original language article. As a result, this study provides no additional support for the efficacy or safety of azelastine nasal spray in the treatment of vasomotor rhinitis. This study is briefly summarized below [Volume 44.6, pages 08.1785-08.1804].

The objective of this study was to investigate the clinical efficacy of azelastine tablets, 1 mg, in the treatment of the symptoms of vasomotor rhinitis. Patients had symptoms suggestive of vasomotor rhinitis and were skin test negative to regional aeroallergens. There was a one-week run-in and baseline evaluation period, followed by a two-week treatment period. Study treatment was azelastine tablets, 1 mg po three times daily. Patients assessed their overall improvement and individual vasomotor rhinitis symptoms

improvement with treatment. Patient-assessed symptoms were sneezing, runny nose, stuffy nose, abnormal sensation of taste, itchy nose, and interference with daily activities. The investigator assessed overall improvement and improvement in the following individual signs with treatment. Investigator-assessed signs were mucosal swelling, color of mucosa, watery secretions, and character of nasal secretions. Safety endpoints included AEs [Volume 44.6, pages 08.1785-08.1789].

Improvement in overall symptoms of vasomotor rhinitis were noted by eight of eleven patients. Improvement was greater for sneezing, runny nose, and stuffy nose. A small amount of improvement was noted in the investigator-assessed signs of vasomotor rhinitis. Watery secretion and mucosal swelling showed the greatest improvement in the investigator-assessment. There was one AE reported, a patient with a moderate skin eruption noted two days after starting study treatment. The eruption resolved within three days after discontinuation of study medication [Volume 44.6, pages 08.1789-08.1804].

8.4. Study 338: A randomized, double-blind, placebo controlled study of the efficacy of azelastine nasal spray in patients with vasomotor rhinitis

First patient enrolled: 11/27/95
Last observation: 5/27/96
Study report dated: 5/7/98

8.4.1. Summary and reviewer's conclusion of study results

This was a randomized, double-blind, placebo controlled, parallel group study performed at 19 centers in France. A study report is provided with the submission. The efficacy variables were poorly defined in this study. There was no definition of the primary efficacy endpoint. The results are also not clearly presented and frequently do not state if the results refer to patient-assessed or investigator-assessed endpoints. As a result, this study does not provide support for efficacy. This study does provide additional support of the safety of azelastine nasal spray in the treatment of symptoms of vasomotor rhinitis. The study is briefly described below.

The objective of this study was to assess the efficacy and tolerance of azelastine nasal spray in the treatment of symptoms of vasomotor rhinitis. Male and female patients, age 15 years and older, were enrolled who had a history of vasomotor rhinitis for at least one year and a negative skin test to aeroallergens [Volume 44.6, page 80.1837]. Study treatments were azelastine nasal spray, 0.14 mg, 1 spray each nostril three times daily and placebo nasal spray, 1 spray each nostril three times daily. The azelastine formulation was identical to the currently approved US product. The European and US pumps have been shown to have comparable performance [Correspondence, 7/24/00, Wallace Laboratories, G. Hemsworth, Ph.D.]. Study treatment was to be given in the morning, at lunchtime, and in the evening. The treatment duration was 15 days.

Efficacy variables were patient- and investigator-assessed change in nasal obstruction, rhinorrhea, sneezing, and anosmia. A visual analogue scale (VAS) was used by patients and investigators to score the severity of symptoms. Changes in rhinoscopy were also

efficacy variables. Safety variables included AEs, hematology, and chemistry studies [Volume 44.6, pages 08.1826-08.1833].

There were 89 patients studied, with 44 in the azelastine group and 45 in the placebo group. Four patients withdrew from the study, two in placebo group for inefficacy and intercurrent disease, and two in azelastine for intolerance and protocol violation (positive skin test) [Volume 44.6, pages 80.1837-08.1838]

A greater decrease in nasal obstruction was observed at day 15 in azelastine-treated patients than in placebo-treated patients. Nasal obstruction and rhinorrhea improved more in the azelastine group than the placebo group [Volume 44.6, page 08.1848]. The study report does not specify if these changes were patient- or investigator-assessed. Nasal mucosal inflammation and edema as assessed by rhinoscopy decreased more in azelastine- than placebo-treated patients [Volume 44.6, page 08.1851]. Patient and investigator global assessments of efficacy and tolerance favored azelastine over placebo [Volume 44.6, page 08.1854].

Only one AE was more common in azelastine-treated patients than placebo and occurred in more than one patient. This AE was bitter taste, which occurred in two azelastine patients and in no placebo patients [Volume 44.6, page 08.1858]. Laboratory studies showed one placebo-treated patient with a slight increase in AST (33 IU/L to 50 IU/L) and ALT (36 IU/L to 100 IU/L) at the end of the study [Volume 44.6, page 08.1860]. There were no azelastine-treated patients with the development of elevated AST or ALT.

9. OVERVIEW OF EFFICACY

The efficacy of azelastine nasal spray in supported by the results of the two pivotal US controlled clinical studies, Study 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 a 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 a 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.

10. OVERVIEW OF SAFETY

10.1. Summary

Safety data from pivotal controlled clinical studies, supporting controlled foreign clinical studies, the sponsor's Summary of Safety, and periodic spontaneous report updates for 5/1/99 through 7/31/99 and 8/1/99-10/31/99 were reviewed to provide this overview of safety. Treatment exposure in the studies included in this application was adequate to assess safety. AEs were more slightly 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. Small numbers of patients with this AE make it difficult to conclude that this is a true safety signal. 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 signal. 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.

Twelve azelastine-treated patients developed elevated AST (SGOT) and/or ALT (SGPT) levels in studies included in this application. These patients were in the pivotal US controlled studies 335 and 336. One azelastine-treated patient developed an AST of 186 IU/mL and ALT of 735 IU/mL. Other patients had mild elevations in AST and/or ALT, with elevations less than twice normal. There were four placebo-treated patients in US clinical studies and one placebo-treated patient in European study 338 that developed elevated AST and/or ALT levels. A search of the AERS database revealed only two cases of elevated transaminases over the 3-1/2 year period since the US approval of this drug.

Both of these cases have confounding medications, and the second case does not have sufficient information to assess causality.

Review of the safety data in this application identifies no other safety concerns. 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.

10.2. Content

The following data were reviewed in the preparation of this overview of safety:

- Safety data from clinical studies included in this application
  - US controlled pivotal Studies 335 and 336
  - Foreign Studies 337 and 338
- The sponsor's Summary of Safety [Volume 44.1, pages 08.6-08.8] and literature survey.
- Periodic safety updates for 5/1/99 through 7/31/99 [NDA 20-114, P-011, 8/27/99] and 8/1/99 through 10/31/99 [NDA 20-114, P-012 , 11/22/99].

Review of these safety data follows.

10.3. Safety data from Clinical Studies 335-338

10.3.1. Exposure

Exposure to azelastine nasal spray in US controlled clinical studies 335 and 336 is described in Table 10.1. These studies used the sponsor's proposed dose, 2 sprays each nostril twice daily. Exposure was to less than 20 days of the 21 day course of azelastine in 11.6 % (25/216) of patients.

Table 8.2.4. Exposure, Studies 335 and 336 [Volume 44.1, page 08.104, Volume 44.4, page 08.1004].

Duration of treatment	Azelastine 2 sprays each nostril twice daily n(%)	
0 to 19 days	25	(11.6)
20 days	15	(6.9)
21 days	79	(36.6)
22 days	70	(32.4)
23 to 29 days	27	(12.5)
Total	216	(100)

Forty-three patients were exposed to 15 days of azelastine nasal spray at the dose of 1 spray each nostril three times daily in French study 338. One patient in this study was exposed to 10 days of medication. Ten patients were exposed to two weeks and one patient two days of azelastine tablets, 1 mg three times daily in Japanese open label study — Exposure to study drug in clinical studies included in this application was adequate to assess safety.

10.3.2. AEs

AEs from studies using the nasal spray formulation of azelastine were integrated and analyzed. These data are presented in Table 10.2. The frequency of AEs were higher in azelastine-treated patients (85.6%, 185/216) than in placebo-treated patients (67.7%,

142/210). 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, dysesthesia, and rhinitis were the most common AEs to have a probable or definite relation to study medication [Volume 44.1, pages 08.69, 08.108, Volume 44.4, pages 08.971, 08.1008]. 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. Although small numbers of patients developed sinusitis, this observation raises the question that azelastine might predispose to the development of bacterial upper respiratory infection. Potential mechanisms for an association of sinusitis with azelastine nasal spray include irritation to the mucosal barrier, thickening of mucus, and/or interference with normal mucociliary function. Small numbers of patients with this AE make it difficult to conclude that this is a true safety signal. Future AEs reports should be monitored for additional instances of sinusitis. It is unlikely that these represent new safety signals.

Table 10.2 Adverse events occurring more commonly in azelastine-treated patients at a rate ≥2% [Volume 44.1, pages 08.106-08.108, Volume 44.4, pages 08.1006-08.1007, Volume 44.6, page 08.1858].

Adverse event	Azelastine N = 216		Placebo N = 210		Total N = 426	
	n	(%)	n	(%)	n	(%)
Taste perversion	42	(19.4)	5	(2.4)	47	(11.0)
Headache	17	(7.9)	16	(7.6)	33	(7.8)
Dysesthesia	17	(7.9)	7	(3.3)	24	(5.6)
Rhinitis	12	(5.6)	5	(2.4)	17	(4.0)
Epistaxis	7	(3.2)	5	(2.4)	12	(2.8)
Sinusitis	7	(3.2)	4	(1.9)	11	(2.6)
Somnolence	7	(3.2)	2	(1.0)	9	(2.1)
All adverse events	185	(85.6)	142	(67.7)	327	(76.8)
All patients with an adverse event	109	(50.5)	81	(38.6)	190	(44.6)

There was one AE reported in the Japanese Study 337. One patient with a moderate skin eruption noted two days after starting study treatment with azelastine tablets 1 mg po three times daily.

Only one AE was more common in azelastine than placebo and occurred in more than one patient in Study 338. This was bitter taste, which occurred in two azelastine patients and in no placebo patients.

10.3.3. SAEs and deaths

There were no SAEs or deaths in any of the clinical studies included in this submission [Volume 44.1, page 08.6, Volume 44.6, page 08.1815].

10.3.4. Withdrawals

There were seven azelastine-treated patients that withdrew from studies with azelastine nasal spray. These withdrawals were two patients with somnolence, and one patient each with taste perversion, back pain, sinusitis, and accidental injury in Studies 335 and 336. One patient in the French clinical trial withdrew for "intolerance", not otherwise specified. These data do not reveal any new safety signal for azelastine nasal spray. [Volume 44.1, pages 08.68, 08.105, Volume 44.26, pages 12.1-12.104, Volume 44.4, page 08.1005, Volume 44.26, pages 12.105-12.308, Volume 44.6, page 08.1837].

10.3.5. Vital signs and physical examination

There were no clinically significant changes in vital signs or body weight in patients in either azelastine or placebo groups in Studies 335 and 336 [Volume 44.1, pages 08.68, 08.103, Volume 44.4, pages 08.970, 08.1003].

There were small numbers of changes in physical examination considered by the investigator to be clinically significant in Studies 335 and 336. Abnormalities of the mouth and throat were seen in six azelastine-treated patients and in one placebo-treated patient in Study 336. These mouth and throat abnormalities were mild and consisted of pharyngitis, cobblestoning, and postnasal drip. The types and frequency of other physical exam abnormalities were similar in azelastine- and placebo-treated groups. Review of these data reveals that these abnormalities were mild and included nasal mucosal edema and erythema, mucus discharge, cervical adenopathy, infraorbital puffiness, middle ear fluid, and wheeze with increased expiratory phase [Volume 44.1, pages 08.67, 08.102, Volume 44.14, pages 11.414-11.635, Volume 44.4, pages 08.969, 08.1002, Volume 44.21, pages 11.2925-11.3127].

Changes in vital signs and physical examination were not assessed in Japanese Study 337 or European Study 338 [Volume 44.6, pages 08.1873-08.1804, 08.1858-08.1859].

Data from vital signs or physical examination from studies included in this application do not reveal any new safety signals.

10.3.6. Laboratory studies

Twelve patients in the azelastine group in the pivotal US clinical studies 335 and 336 developed elevated AST (SGOT) and/or ALT (SGPT) levels. A listing of these patients is presented in Table 10.3. One azelastine-treated patient, #53 at Study Center 980006, had an AST of 186 IU/mL and ALT of 735 IU/mL at Visit 4. The AST and ALT fell to 30 and 71 IU/mL, respectively, ten days later despite continued use for vasomotor rhinitis symptoms [Volume 44.1, pages 08.69-08.71]. Other patients had mild elevations in AST and/or ALT, with elevations less than twice normal. There were four placebo-treated patients in US clinical studies and one placebo-treated patient in European study 338 that developed elevated AST and/or ALT levels after treatment.

Table 10.3. Increase in AST (SGOT) and ALT (SGPT) in azelastine-treated patients, Studies 335, 336, and 338*.

Azelastine-treated patients							
Study Center	Patient	AST, IU/mL**			ALT, IU/L**		
Study 335		Baseline	Visit 4	Follow-up	Baseline	Visit 4	Follow-up
980006	53	21	186	30	16	735	71
980017	262	19	168	59	18	67	67
980011	155	20	37	ND	8	33	ND
980013	185	31	45	ND	24	53	ND
980014	204	24	33	ND	41	55	ND
980014	208	16	32	ND	17	41	ND
980017	268	24	37	ND	29	40	ND
980018	285	22	31	ND	37	57	ND
Study 336							
980025	28	24	40	ND	23	28	ND
980028	90	19	69	ND	21	84	ND
980033	192	28	33	ND	40	53	ND
980037	273	34	42	ND	34	38	ND
Placebo-treated patients							
Study Center	Patient	AST, IU/mL			ALT, IU/L		
Study 335		Baseline	Visit 4	Follow-up	Baseline	Visit 4	Follow-up
	None						
Study 336							
980025	23	24	32	ND	29	50	ND
980028	91	19	26	ND	37	52	ND
980031	152	24	29	ND	32	51	ND
980036	242	27	31	ND	31	42	ND
Study 338							
	33	33	50	ND	36	100	ND

*[Volume 44.1, pages 08.69-08.71, Volume 44.15, pages 11.755-11.756, 11.759-11.761, 11.902-11.903, 11.1192-1194, Volume 44.22, pages 11.3254-11.3255, 11.3282-11.3283, 11.3360-11.3361, 11.3385-3387, 11.3462-11.3463, 11.3511-11.35412, 11.3588-11.3589, 11.3615-11.3616]

**Laboratory normal ranges: AST Males 11-36 IU/mL, Females 6-34 IU/mL ALT Males 6-43 IU/mL, Females 6-43 IU/mL
[Volume 44.15, page 11.728, Volume 44.21, page 11.3223]

This reviewer searched the AERS database on 8/4/00 for similar spontaneous reports. AERS was searched with the following search strategy: Primary NDA/Trade Name = N 20-114, Astelin AND Primary ingredient = azelastine AND Reaction = Hepatobiliary investigations AND Reaction = Hepatobiliary disorders. Astelin® Nasal Spray was originally approved in the US on 11/1/96. This search revealed only two reported cases over this 3-1/2 year period. The first case, AERS #3494932, was a 44 year old man with hepatitis and elevated transaminases. This patient was taking higher than the recommended dose of bromfenac, in addition to azelastine nasal spray, Excedrine, and lansoprozole. He had a history of alcohol abuse and occupational exposure to carbon tetrachloride and organotin, both of which are hepatotoxins. This case was published as a case of bromfenac-induced centrilobular necrosis[7]. The second case, AERS #3337064, was a 67 year-old woman that developed elevated AST while taking azelastine, Levbid® (hyoscyamine), and glucosamine sulfate. The severity of AST elevation was not noted. Both of these cases have confounding medications, and the second case does not have sufficient information to assess causality.

A slightly higher rate of elevated AST and/or ALT was noted in figures in Dr. Himmel's original NDA review of azelastine [Medical Officer review, NDA 20-114, 7/19/93, pages

[7] Cortes-Belen E, Benitez JG, Verrico P. Bromfenac-induced centri-lobular necrosis. J Toxicol Clin Toxicol 1998; 36[5, Suppl]: 447, abstr:50.

70-71]. His review also notes that preclinical data showed elevated levels of AST, ALT, reversible fatty changes in the liver, and hepatocellular hypertrophy at doses of 30 mg/kg/day [Medical Officer review, NDA 20-114, 7/19/93, page 6].

Infrequent occurrences of elevated transaminases are noted in the current product label for Astelin® Nasal Spray. This reviewer does not believe there is a need for changing the label at this time because of the low degree of AST and ALT elevation noted in these studies and because of the lack of additional clear-cut spontaneous reports over the 3-1/2 year period that the product has been marketed in the US.

There were no other laboratory study abnormalities that developed in azelastine-treated patients that were consistently seen in studies in this application.

10.4. ECGs

ECGs were not performed in studies included in this application. ECG data from prior studies supporting the SAR indication of azelastine nasal spray also support this application.

10.5. Spontaneous AE reports

Spontaneous AE reports in the pediatric population were reviewed recently for the pediatric efficacy supplement for Astelin® Nasal Spray. A summary of spontaneous AE reports was not submitted with this application. Separately 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 [NDA 20-114, P-011, 8/27/99 and NDA 20-114, P-012 , 11/22/99].

10.6. Literature survey

A search of the published literature identified a single study describing the use of azelastine in the treatment of vasomotor rhinitis [Volume 44.1, page 08.2]. This paper was included in this application as Study 337 and is reviewed in Section 8.3. of this review. There was one AE reported, a patient with a moderate skin eruption noted two days after starting study treatment. This literature survey does not identify new safety concerns.

11. SPECIAL POPULATIONS

Evaluation of efficacy and safety was performed only on the two pivotal clinical studies 335 and 336 because complete study reports for Studies 337 and 338 were not included with the application.

11.1. Efficacy

There was no difference in efficacy between men and women for the primary efficacy endpoint, the TVRSS, in either of the two pivotal controlled clinical studies [Volume 1.184, page 1 and Table 1, page not numbered].

A majority of patients in both clinical studies were Caucasian. The small number of non-Caucasians precluded any meaningful treatment by race analysis of efficacy [Volume 44.1, page 08.81, Volume 44.13, pages 11.1-11.8, Volume 44.4, page 08.982, Volume 44.20, pages 11.2529-11.2535].

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 in these age groups. 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 [Volume 44.4, pages 08.1198-08.1209, Volume 44.2, pages 08.316-08.337]. These data are displayed in Table 11.1.

Table 11.1. Analysis of efficacy, Overall difference in TVRSS, patients ages 12-15 years, Studies 335 and 336 [Volume 44.2, pages 08.316-08.337, Volume 44.4, pages 08.1198-08.1209]

Azelastine					Placebo				
Center	Patient	Baseline	Overall	Difference	Center	Patient	Baseline	Overall	Difference
Study 335									
Mean overall difference in TVRSS				-0.98					-1.04

11.2. Safety

Women had higher rates of taste perversion, headache, dysesthesia, rhinitis, epistaxis, and somnolence than men in the two pivotal clinical studies. Of these AEs, dysesthesia, rhinitis, sinusitis, and somnolence occurred more frequently in women taking azelastine than placebo. Small numbers of patients make it difficult to conclude that these are gender-specific AEs. Men and women had similar rates of pharyngitis and sinusitis [NDA 20-114, SE5-006 BM, 2/11/00, Table 2, page not numbered]. These data are presented in Table 11.2.

Table 11.2. Analysis of safety, AEs by gender, Studies 335 and 336 [Volume 44.4, pages 08.1198-08.1209, NDA 20-114, SE5-006 BM, 2/11/00, Table 2, page not numbered]

Adverse event	Men				Women			
	Azelastine N = 54		Placebo N = 61		Azelastine N = 162		Placebo N = 149	
	n	(%)	n	(%)	n	(%)	n	(%)
Taste perversion	8	(15)	0	(0)	34	(21)	5	(3)
Headache	1	(2)	6	(10)	16	(10)	10	(7)
Dysesthesia	0	(0)	0	(0)	17	(10)	7	(5)
Pharyngitis	3	(6)	0	(0)	9	(6)	12	(8)
Rhinitis	0	(0)	2	(3)	12	(7)	3	(2)
Epistaxis	1	(2)	1	(2)	6	(4)	4	(3)
Sinusitis	2	(4)	3	(5)	5	(3)	1	(1)
Somnolence	1	(2)	1	(2)	6	(4)	1	(1)

A majority of patients in both clinical studies were Caucasian. The small number of non-Caucasians precluded any meaningful treatment by race analysis of safety.

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. These data are presented in Table 11.3.

Table 11.3. Analysis of safety, AEs in patients ages 12-15 years, Studies 335 and 336 [Volume 44.19, pages 11.2077-11.2089, Volume 44.24, pages 11.4468-11.4477]

Azelastine			Placebo		
Center	Patient	AE	Center	Patient	AE
Study 335					
980005	36	Dysesthesia	980004	14	None
980006	47	Pharyngitis, sinusitis	980009	108	Nausea, URI
980006	48	None	980010	124	None
980006	49	None	980016	248	None
980006	52	None	980016	249	None
980010	131	None	980017	277	Headache
			980017	280	Headache
Study 336					
980028	95	URI	980027	75	Dyspepsia
980029	101	Paresthesia, taste perversion	980030	121	None
980033	187	None	980038	288	None
980037	361	Somnolence			

12. DSI AUDIT AND FINANCIAL DISCLOSURE

Two sites from the efficacy studies were reviewed by DSI. The sites were: (1) William E. Berger, Mission Viejo, CA, for Study 335, and (2) Jonathan Matz, M.D., Baltimore, MD, for Study 336. Representative data from the NDA were provided to the DSI team for comparison with the original data source. Data were verified at both sites. Discrepancies noted at Dr. Berger's site included lack of documentation of unused study drug at the close of therapy. Discrepancies noted at Dr. Matz's site included inadequate drug dispensing records, failure to exclude one patient due to use of a prohibited medication, and inadequate documentation of dates of AEs for five patients and concomitant medications for two subjects. Despite the discrepancies, the DSI inspectors concluded that the data for both sites appeared acceptable for use in support of drug claims [Correspondence from DSI, May 30, 2000 and June 9, 2000].

[ ]

The sponsor states that the randomized, double-blind, multicenter, placebo-controlled design of the study, computer generated randomization of patients to treatment groups, and validation of the Case Report Form minimize the potential for bias in clinical study results [Volume 44.1, Form FDA 3454 and following pages, not numbered]. This reviewer concurs that the study design and conduct minimizes potential bias and that the data is suitable for review.

13. REVIEW OF PROPOSED PRODUCT LABELING

The sponsor provided paper and electronic copies of the proposed product labeling [N20-114, C, 1/28/00, pages not numbered]. The sponsor's proposed product labeling is attached to this review as Appendix. Preliminary review of the proposed labeling follows. Final labeling will be negotiated with the sponsor.

The heading of the section or subsection requiring revision is followed by this reviewer's comments and suggested language.

1. DESCRIPTION

Reviewer comment:
The molecular formula is written as $C_{22}H_{24}ClN_3O{\cdot}HCl$, [redacted] atom per molecule. This is a typographic error and should be corrected to $C_{22}H_{24}ClN_3O{\cdot}HCl$, with two chlorine atoms per molecule.

2. CLINICAL PHARMACOLOGY
Special Populations

Reviewer comment:
The second paragraph gives a definition of renal insufficiency as ' [redacted] clearance <50mL/min." [redacted] is a typographic error and the definition should be "creatinine clearance <50 mL/min."

3. CLINICAL PHARMACOLOGY
Clinical Trials

Reviewer comment:
This paragraph should be changed to reflect the inclusion criteria in these studies. The words [redacted] ' should be changed to "comprised of" because there were no other symptoms used to calculate the symptom complex and the words [redacted] Sneezing should be moved to a less prominent position in the last sentence because patients with vasomotor rhinitis report this symptom less commonly than the others listed:

Suggested language:
Two hundred sixteen patients with vasomotor rhinitis received Astelin Nasal Spray two sprays per nostril twice a day in two US placebo controlled trials. These patients had vasomotor rhinitis for at least one year, negative skin tests to indoor and outdoor aeroallergens, negative nasal smears for eosinophils, and negative sinus X-rays. Astelin Nasal Spray significantly improved a symptom complex comprised of rhinorrhea, post nasal drip, nasal congestion, and sneezing.

4. INDICATIONS AND USAGE

Reviewer comment:
The diagnosis should be worded as vasomotor rhinitis to remain consistent throughout the label. In addition, [redacted] should be removed from the vasomotor rhinitis clause of the sentence because patients with vasomotor rhinitis report this symptom less commonly than the others listed. This section should read as follows:

Suggested language:

[redacted]

5. PRECAUTIONS
Geriatric Use

Reviewer comment:
The Geriatric Use subsection should be revised in accordance with the specific requirements on the content and format of labeling found in 21 CFR 201.57(f)(10). This regulation pertains to use of drug in persons 65 years of age and older. Recommended language for this subsection is presented in this regulation. The sponsor has been asked to rewrite this section.

6. ADVERSE REACTIONS

Seasonal Allergic Rhinitis

Reviewer comment:
The heading [redacted] should be changed to "Seasonal Allergic Rhinitis." As written, this heading could be interpreted as including [redacted] an indication for which the product is not approved.

7. ADVERSE REACTIONS
Seasonal Allergic Rhinitis

Reviewer Comment:
A [redacted] is listed for the adverse events in the table for AEs observed in SAR studies. The [redacted] should be deleted because inferential statistics should only be performed on prospectively defined endpoints.

8. ADVERSE REACTIONS

Vasomotor Rhinitis

Reviewer comment:
These comments refer to the sponsor's entire proposed Adverse Reaction section for vasomotor rhinitis:

[redacted] should be deleted from the subheading to make the indication consistent with the rest of the label. The [redacted] in the table in this section should be deleted because inferential statistics should be performed only on prospectively defined endpoints. This reviewer totaled AEs for Studies 335 and 336 and obtained different AE rates than those displayed in the sponsor's table. The list of infrequently observed events should be deleted because they occurred in four patients or less and add no useful information. Some of these events are noted in other sections of the label. The sponsor proposed removing [redacted] Diarrhea, paresthesia, and xerophthalmia should remain in this section because the text immediately below the vasomotor rhinitis AE table should be deleted.

This section should read as follows. [redacted]

Suggested language:
ADVERSE REACTIONS
Vasomotor Rhinitis
Adverse experience information for Astelin® Nasal Spray is derived from two placebo-controlled clinical studies which included 216 patients who received Astelin® Nasal Spray at a dose of 2 sprays per nostril twice daily for up to 28 days. The incidence of discontinuation due to adverse reactions in patients receiving Astelin® Nasal Spray was not different from vehicle placebo (2.8% vs 2.9%, respectively).

The following adverse events were reported with frequencies ≥2% in the Astelin® Nasal Spray treatment group and more frequently than placebo.

ADVERSE EVENT	Astelin® Nasal Spray n = 216	Vehicle Placebo n = 210
Bitter Taste	19.4	2.4
Headache	7.9	7.6
Dysesthesia	7.9	3.3
Rhinitis	5.6	2.4
Epistaxis	3.2	2.4
Sinusitis	3.2	1.9
Somnolence	3.2	1.0

Events observed infrequently (<2% and exceeding placebo incidence) in patients who received Astelin® Nasal Spray (2 sprays/nostril twice daily) in U.S. clinical trials in vasomotor rhinitis were similar to those observed in U.S. clinical trials in seasonal allergic rhinitis.

In controlled trials involving nasal and oral azelastine hydrochloride formulations, there were infrequent occurrences of hepatic transaminase elevations. The clinical relevance of these reports has not been established.

In addition, the following spontaneous adverse events have been reported during the marketing of Astelin® Nasal Spray and causal relationship with the drug is unknown:

anaphylactoid reaction, application site irritation, chest pain, nasal congestion, confusion, diarrhea, dyspnea, facial edema, involuntary muscle contractions, paresthesia, parosmia, pruritus, rash, tolerance, urinary retention, and vision abnormal and xerophthalmia.

APPENDIX

Sponsor's Proposed Product Labeling

Proposed product labeling is found in the following section.

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 11 PAGES

Draft

Labeling

/S/ 8/25/00

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/ 8/25/00

Badrul A. Chowdhury, M.D., Ph.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: HFD-570/Division File
HFD-570/Lee/Medical Reviewer
HFD-570/Chowdhury/Team Leader
HFD-570/Meyer/Division Director
HFD-715/Wilson/Biometrics Team Leader
HFD-570/Trout/Project Manager

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