hours 2-5 showed similar results with a statistically significant reduction in MSC between CTC vs. TF Sinus ($p < 0.001$), CTC vs. placebo ($p < 0.001$), and no difference between TF Sinus and placebo ($p=0.657$).

Table 8.2.9 Average reduction from baseline, MSC score at hours 2- 5 [Volume 1.29, pages 18, 19, 88-89]

Treatment group	N	Baseline MSC (SD)	Absolute change (SD)*	Percent change (SD)*	Comparison**	p-value***
Dose 1						
CTC	118	12.74 (6.10)	6.61 (4.34)	50.02 (38.6)	CTC vs. TF Sinus	0.002
TF Sinus	119	14.03 (6.10)	4.88 (4.36)	34.23 (38.6)	CTC vs. Placebo	0.023
Placebo	61	13.02 (5.89)	4.90 (4.37)	36.38 (38.7)	TF Sinus vs. Placebo	0.720
Dose 2						
CTC	118	12.74 (6.10)	8.41 (4.54)	63.73 (37.8)	CTC vs. TF Sinus	<0.001
TF Sinus	119	14.03 (6.10)	6.02 (4.56)	43.38 (37.6)	CTC vs. Placebo	<0.001
Placebo	61	13.02 (5.89)	5.70 (4.53)	42.43 (37.7)	TF Sinus vs. Placebo	0.871

*SD calculated from the formula SD = SE(square root of N)
**Comparison based on percent reduction from baseline in MSC
***ANCOVA

8.2.4.7.b. Secondary efficacy variables

Results of secondary efficacy variables support the efficacy of CTC. The primary comparison was CTC versus TF Sinus. Onset of efficacy was 2 hours after Dose 1 and efficacy was maintained throughout the 6 hour dosing interval. CTC decreased MSC and TSC scores over hours 1 to 6 and TSC over hours 2 to 5 more than TF Sinus and placebo after both doses of treatment medication. Patient global assessment of efficacy showed CTC superior to TF Sinus and placebo. Results for each of the secondary efficacy variables for this study are described below:

- Average reduction from baseline in MSC over hours 1 to 6 after each dose [Volume 1.29, pages 100-101, 110-111]
  After Dose 1, the average reduction from baseline in the MSC over hours 1 to 6 was 6.24 for CTC, 4.54 for TF Sinus, and 4.63 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 1 to 6 after Dose 1 of study medication.

  After Dose 2, the average reduction from baseline in the MSC over hours 1 to 6 was 8.30 for CTC, 6.00 for TF Sinus, and 5.58 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 1 to 6 after Dose 2 of study medication.

  An improvement in the placebo group was noted after both doses due to the placebo effect, regression toward the mean or other cause for abatement in SAR symptoms.

- Average reduction from baseline in TSC over hours 2 to 5 after each dose [Volume 1.29, pages 92, 96]

After Dose 1, the average reduction from baseline in the TSC over hours 2 to 5 was 11.11 for CTC, 8.57 for TF Sinus, and 8.25 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 2 to 5 after Dose 1 of study medication.

After Dose 2, the average reduction from baseline in the TSC over hours 2 to 5 was 14.23 for CTC, 10.55 for TF Sinus, and 9.78 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 2 to 5 after Dose 2 of study medication.

An improvement in the placebo group was noted after both doses due to the placebo effect or other cause for abatement in SAR symptoms.

- Average reduction from baseline in TSC over hours 1 to 6 after each dose [Volume 1.29, pages 120-121, 130-131]
  After Dose 1, the average reduction from baseline in the TSC over hours 1 to 6 was 10.53 for CTC, 7.99 for TF Sinus, and 7.83 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 1 to 6 after Dose 1 of study medication. [Volume 1.29, pages 120-121, 130-131]

  After Dose 2, the average reduction from baseline in the TSC over hours 1 to 6 was 14.04 for CTC, 10.51 for TF Sinus, and 9.43 for placebo, indicating superior efficacy of CTC compared with TF Sinus and placebo. There was little difference between the TF Sinus group and the placebo group for this variable. Similar results were seen with a comparison of the percent change from baseline in the MSC scores over hours 1 to 6 after Dose 2 of study medication.

  An improvement in the placebo group was noted after both doses due to the placebo effect or other cause for abatement in SAR symptoms.

- Time point by time point comparison of MSC and TSC
  Statistically significant decreases were seen in the MSC in the CTC group when compared with the placebo group, starting 2 hours after Dose 1 of medication, with continued efficacy until the end of the dosing interval 6 hours post-dose. Efficacy was maintained with significant decreases in the MSC in the CTC compared with the placebo group at all time points after Dose 2 of medication. These data are displayed in Tables 8.2.10 and 8.2.11. Onset of action of the drug was seen with the MSC at 2 hours post-dose and efficacy was maintained throughout the dosing interval after both doses of medication.

Similar findings were seen when comparing CTC vs. TF Sinus, with a significant difference noted at 0.5 hours after Dose 1 of medication. This difference was maintained at all time points following both doses of medication. [Volume 1.30, pages 51, 100-101]

Table 8.2.10 Time point by time point change in MSC after Dose 1 of study medication, HSC-306 [Volume 1.29, page 100-101]

Hours after Dose 1	Treatment	N	MSC, Mean change	SE	Comparison	p-value*
0.5	CTC	118	2.03	0.37	CTC vs. TF Sinus	0.003
	TF Sinus	119	0.51	0.37	CTC vs. Placebo	0.727
	Placebo	61	2.24	0.52	TF Sinus vs. Placebo	0.006
1.0	CTC	118	3.83	0.39	CTC vs. TF Sinus	0.038
	TF Sinus	118	2.71	0.39	CTC vs. Placebo	0.634
	Placebo	61	3.52	0.54	TF Sinus vs. Placebo	0.214
2.0	CTC	118	5.58	0.44	CTC vs. TF Sinus	0.029
	TF Sinus	118	4.24	0.44	CTC vs. Placebo	0.030
	Placebo	61	3.97	0.61	TF Sinus vs. Placebo	0.722
3.0	CTC	118	6.34	0.45	CTC vs. TF Sinus	0.023
	TF Sinus	118	4.93	0.45	CTC vs. Placebo	0.023
	Placebo	61	4.63	0.62	TF Sinus vs. Placebo	0.695
4.0	CTC	118	6.87	0.47	CTC vs. TF Sinus	0.005
	TF Sinus	118	5.01	0.47	CTC vs. Placebo	0.039
	Placebo	61	5.24	0.65	TF Sinus vs. Placebo	0.764
5.0	CTC	118	7.61	0.45	CTC vs. TF Sinus	<0.001
	TF Sinus	118	5.33	0.45	CTC vs. Placebo	0.014
	Placebo	61	5.75	0.62	TF Sinus vs. Placebo	0.578
6.0	CTC	118	6.24	0.37	CTC vs. TF Sinus	0.001
	TF Sinus	118	4.54	0.37	CTC vs. Placebo	0.010
	Placebo	61	4.63	0.52	TF Sinus vs. Placebo	0.886

*ANCOVA T-Test was the test of statistical significance

Table 8.2.11 Time point by time point change in MSC after Dose 2 of study medication, HSC-306 [Volume 1.29, page 100]

Hours after Dose 2	Treatment	N	MSC, Mean change	SE	Comparison	p-value*
1.0	CTC	117	8.08	0.48	CTC vs. TF Sinus	0.021
	TF Sinus	118	6.54	0.47	CTC vs. Placebo	0.002
	Placebo	61	5.61	0.66	TF Sinus vs. Placebo	0.240
2.0	CTC	117	8.21	0.48	CTC vs. TF Sinus	0.007
	TF Sinus	118	6.39	0.48	CTC vs. Placebo	0.005
	Placebo	61	5.93	0.66	TF Sinus vs. Placebo	0.564
3.0	CTC	115	8.35	0.48	CTC vs. TF Sinus	<0.001
	TF Sinus	117	5.63	0.47	CTC vs. Placebo	<0.001
	Placebo	61	5.16	0.65	TF Sinus vs. Placebo	0.557
4.0	CTC	115	8.60	0.46	CTC vs. TF Sinus	<0.001
	TF Sinus	117	5.81	0.45	CTC vs. Placebo	<0.001
	Placebo	61	5.84	0.63	TF Sinus vs. Placebo	0.964
5.0	CTC	115	8.35	0.46	CTC vs. TF Sinus	<0.001
	TF Sinus	118	6.12	0.45	CTC vs. Placebo	0.001
	Placebo	61	5.89	0.62	TF Sinus vs. Placebo	0.758
6.0	CTC	115	8.10	0.50	CTC vs. TF Sinus	<0.001
	TF Sinus	117	5.43	0.49	CTC vs. Placebo	<0.001
	Placebo	61	5.11	0.69	TF Sinus vs. Placebo	0.698

*ANCOVA T-Test was the test of statistical significance

Similar findings were present with the TSC. Statistically significant decreases in TSC in the CTC group in comparison with the placebo group were seen starting 2 hours after Dose 1 of medication, with continued efficacy until the end of the dosing interval 6 hours post-dose. Efficacy was maintained with significant decreases in the TSC in the CTC compared with the placebo group at all hourly time points after Dose 2 of medication. Onset of action of the drug was seen with the TSC at 2 hours post-dose and efficacy was maintained throughout the dosing interval after both doses of medication.

Similar findings were seen when comparing the TSC with CTC vs. TF Sinus. A significant difference was noted at in the TSC 0.5 hours after Dose 1 of medication. This difference was maintained at all time points following both doses of medication. [Volume 1.30, pages 51, 130-131]

An improvement in the placebo group due to the placebo effect or other cause for abatement in SAR symptoms was noted after both doses with the MSC and the TSC at each time point.

- Time point by time point comparisons of individual symptoms
  CTC was more effective in treating the symptoms of allergic rhinitis than placebo or TF Sinus. CTC was better than TF Sinus for itchy nose, runny nose, watery eyes, itchy throat, nose blows, and postnasal drip at seven or more of the time points during the study. CTC was better than placebo in the treatment of sniffles, postnasal drip, headache, itchy nose, and runny nose at seven or more of the 13 time points during the study. After Dose 1, sustained efficacy of CTC compared with placebo was seen first starting at hour 1 for postnasal drip and 3 hours after Dose 1 for itchy nose, and efficacy was maintained until the end of the dosing interval. Sustained efficacy was seen starting at hour 5 for runny nose, sniffles, and headache and efficacy was maintained until the end of the dosing interval. Efficacy of CTC compared with placebo was seen with cough starting at hour 3, but was not maintained until the end of the dosing interval. [Volume 1.30, page 53]

- Global assessment of efficacy at Visit 3
  Patients in the CTC group rated the effectiveness of their treatment higher than the placebo and TF Sinus groups. There was a placebo effect noted with a mean improvement of 1.66 in the placebo group. These data are displayed in Table 8.2.12.

Table 8.2.12 Patient global assessment of efficacy [Volume 1.29, page 266]

Treatment	N	Mean
CTC	115	2.38
TF Sinus	118	2.04
Placebo	60	1.66

8.2.4.8. Safety outcomes

The safety variable for this study was adverse events (AEs). Vital signs and physical examination were performed only at screening and were therefore not safety variables for this study. There were no laboratory studies performed as safety variables for this study. Pregnancy tests were performed as inclusion/exclusion criteria and ECGs were not performed in this study.

This study supports the safety of CTC in the treatment of the symptoms of SAR. AEs were fairly frequent in this study and were more frequent in CTC-treated patients than TF Sinus-treated patients and placebo-treated patients. Somnolence and fatigue were the most common AEs in CTC treated patients. AEs occurring in CTC-treated patients were moderate in severity, except for somnolence and fatigue, for which some severe AEs were noted. There were no deaths or SAEs in this study and there were no withdrawals from this study due to AEs which are discussed in detail below.

8.2.4.8.a. Total drug exposure

Total exposure to CTC may be estimated from compliance data, and was almost perfect. Patient 2064 only had one dose of CTC. A total of 117 patients of the 118 randomized to CTC were exposed to two doses. All 118 patients randomized to CTC had at least one dose.

8.2.4.8.b. Adverse events (AEs)

AEs were fairly frequent in this study and were more frequent in CTC-treated patients than in TF Sinus-treated patients and placebo-treated patients. These data are presented in Table 8.2.13. There were 40 AEs in 118 CTC-treated patients (33.9%), compared with 31 AEs in 119 TF Sinus-treated patients (26.1%), and 11 AEs in 61 placebo-treated patients (18.1%). AEs occurring in CTC-treated patients moderate in severity, except for somnolence and fatigue, for which some severe AEs were noted. Somnolence was common in CTC-treated patients (18.6%, 22/118) and was more frequent than in TF Sinus-treated patients (5.9%, 7/119) and placebo-treated patients (0/61, 0%). Of these 22 AEs from somnolence in CTC-treated patients, 6 were mild, 13 were moderate, and 3 were severe. Fatigue was common in CTC-treated patients (5.1%, 6/118), was similar in frequency to TF Sinus-treated patients (7/119, 5.9%), and was more frequent than in placebo-treated patients (1.6%, 1/61). Of these 6 AEs from fatigue in CTC-treated patients, 5 were moderate in severity and one was severe. Headache was less common in CTC-treated patients (0.8%, 1/118) than in placebo-treated patients (4.9%, 3/61) and was similar in frequency to TF Sinus-treated patients (1.7%, 2/119). This may represent a treatment effect for CTC and TF Sinus, but this difference between treatment groups could also be explained by normal variation among small numbers of patients. Nervousness was not seen in TF sinus or placebo, but was reported in two CTC patients (1.7%, 2/118). [Volume 1.29, page 20]

Table 8.2.13 HSC-306, adverse events occurring in more than one patient taking clemastine and more frequently than placebo [Volume 1.29, page 20]

Adverse Event	CTC N=118		TF Sinus N=119		Placebo N=61	
	n	(%)	n	(%)	n	(%)
Somnolence	22	(18.6)	7	(5.9)	0	(0)
Fatigue	6	(5.1)	7	(5.9)	1	(1.6)
Nervousness	2	(1.7)	0	(0)	0	(0)
Headache*	1	(0.8)	2	(1.7)	3	(4.9)
All events	40	(33.9)	31	(26.1)	11	(18.1)

*Headache included in this table even though it was reported in only one CTC patient and was more frequent than placebo because of the difference between CTC and placebo

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

Although not explicitly stated, review of individual AEs reveal that there were no deaths or SAEs in this study.

8.2.4.8.d. Withdrawals due to AEs

There were no withdrawals from this study because of AEs. [Volume 1.29, page 54]

8.2.4.8.e. Vital signs

Vital signs and physical examination were not safety variables for this study were not performed at the close of the study.

8.2.4.8.f. Laboratory studies

There were no laboratory studies performed as safety variables in this study. Pregnancy tests were performed as inclusion/exclusion criteria for this study.

8.2.4.8.g. ECGs

ECGs were not performed in this study.

8.3. HSC-303: A double-blind, placebo controlled, randomized, crossover study to evaluate the efficacy of single doses of 0.25 mg, 0.5 mg, and 1.0 mg clemastine syrup and placebo in the inhibition of wheal and flare response following intradermal histamine injections

8.3.1. Summary and reviewer's conclusion of study results

This was a double blind, four period, crossover study, performed in a total of 24 healthy male subjects, ages 18-50 years. The objective of this study was to evaluate the antihistamine effects of clemastine syrup and placebo syrup on the inhibition of the wheal and flare response to intradermal skin tests with histamine in healthy male subjects. The purpose of this study in the sponsor's drug development plan was to establish the minimal effective dose of clemastine. Study treatments were placebo and 0.25 mg, 0.5 mg, and 1.0 mg of clemastine. There was a seven day washout between each period of the study. The primary efficacy variable was the mean change from baseline in wheal and flare size after the four treatments. Safety endpoints were AEs, vital signs, physical examination, hematology, chemistry, urinalysis, and ECGs.

A dose-related suppression of wheal size was noted for the 0.5 mg and 1.0 mg doses of clemastine at 4 hours post-dose, and was suggested at 2 hours post-dose. Peak suppression of wheal size for the 0.5 mg and 1.0 mg doses of clemastine was noted at 8 hours post-dose. A dose-related suppression in flare size was noted for the 0.5 mg and 1.0 mg doses of clemastine. Suppression of flare size was noted for the 0.25 mg dose of clemastine only at 8 hours post-dose. Peak suppression of flare size for the 0.5 mg dose of clemastine was noted at 6 hours post-dose and peak flare size suppression for the 1.0 mg dose of clemastine was at 8 hours post-dose.

There were 10 AEs in 24 subjects. There were seven AEs in 18 clemastine treated subjects (38.9%) and two AEs in 6 placebo-treated subjects (50.0%). AEs occurring in more than one clemastine-treated patient were cough and rhinitis, which occurred in two patients each (11.1%). There were no deaths or SAEs. There were no clinically significant changes in vital signs, physical examination, hematology, chemistry, urinalysis, or ECGs.

It should be noted that histamine skin test suppression has limited clinical correlation and is not valid as a surrogate for symptom control. In this reviewer's opinion, limited information can be drawn from the efficacy results of this study. This study supports the safety of clemastine.

8.3.2. Objective/Rationale

The objective of this study was to evaluate the antihistamine effects of 0.25 mg, 0.5 mg, and 1.0 mg of clemastine syrup and placebo syrup on the suppression of the wheal and flare response to intradermal skin tests with histamine in healthy male subjects. [Volume 1.23,

page 180] The purpose of this study in the sponsor's drug development plan was to establish the minimal effective dose of clemastine.

8.3.3. Protocol

This was a double blind, four period, crossover study, performed in a total of 24 healthy male subjects, ages 18-50 years. Subjects were randomly assigned to one of four dosing sequences of placebo and 0.25 mg, 0.5 mg, and 1.0 mg of clemastine. There was a seven day washout between each period of the study. [Volume 1.23, pages 180-181]

Subjects were screened no more than 14 days before the start of the study. Subjects were males from 18 to 50 years of age. Subjects were to have no prescription drugs for 14 days prior to the study and no non-prescription drugs for seven days prior to the study. Subjects were to have a normal response to intradermal skin tests with saline and histamine. The normal response to saline skin test was defined as a wheal size <1.0 mm with no flare at 15 minutes. The normal response to histamine skin test was defined as a wheal size greater than that of the saline wheal size with a flare of >20 mm [Volume 1.23, pages 182-184]. Subjects were skin tested on the back. Skin test sites on the back were randomly assigned. [Volume 1.23, page 186]

The histamine skin test was performed with [redacted] mg histamine base/ml, 0.05 mL given intradermally, which delivered a total of [redacted] mcg histamine base. The saline skin test was performed with 0.05 mL given intradermally. [Volume 1.23, pages 186, 188] The skin test site was measured 15 minutes after injection and the margins of the wheal and flare were traced onto clear tape for measurement of area. Skin tests were performed and measurements were taken at baseline and at 2, 4, 6, 8, and 12 hours after administration of study treatment [Volume 1.23, page 187]

The primary efficacy variable was the mean change from baseline in wheal and flare size after the four treatments. Clemastine and placebo were administered as a syrup. Safety variables were AEs, vital signs, physical examination, hematology, chemistry, urinalysis, and ECGs [Volume 1.23, page 181].

8.3.4. Results

8.3.4.1. Demographics, Protocol Violations, Withdrawals

Twenty-four males were enrolled in this study, and all completed the four treatment periods [Volume 1.23, pages 40, 49]. The average age of subjects was 28.5 years with a range of 19-45 years. All subjects were Caucasian except for one subject who was Hispanic.

There were minor protocol deviations in this study. Two subjects had loss of 1-2 drops of study medication at dosing and one subject had the baseline skin test measurement one minute late [Volume 1.23, pages 40-41]. These protocol deviations were not likely to influence the efficacy or safety analysis.

8.3.4.2. Efficacy variable outcomes

Baseline wheal sizes for the 0.5 mg and 1.0 mg doses of clemastine were larger than the 0.25 mg dose and placebo. A dose-related suppression of wheal size was noted for the 0.5 mg and 1.0 mg doses of clemastine. Suppression of wheal size was noted for the 0.5 mg and 1.0 mg doses of clemastine at 4 hours post-dose, and was suggested at 2 hours post-dose. Suppression of the wheal size with 0.5 mg and 1.0 mg of clemastine continued to the 12 hours post-dose time point. Peak suppression of wheal size for the 0.5 mg and 1.0 mg doses of clemastine was at 8 hours post-dose. There was no consistent suppression of wheal size noted with the 0.25 mg dose of clemastine. There was a dose response effect noted at 4, 6, and 12 hours post-dose. These data are displayed in Table 8.3.1.

The study reports notes a sequence by treatment interaction for wheal size at 4 hours [Volume 1.23, pages 27, 41-42]. In light of the seven day washout between single doses of this antihistamine this is not likely to be a true effect, but more likely a vagary of the small sample size, and possibly a result of the difference in baseline wheal sizes.

Table 8.3.1 HSC-303, change from baseline in wheal size [Volume 1.23, page 57]

Treatment	Baseline, mm2	Change from baseline, mm2				
	0 hours	2 hours	4 hours	6 hours	8 hours	12 hours
Placebo	174.86	5.77	-3.98	4.65	-2.32	22.79
0.25 mg clemastine	172.94	2.10	-13.33	-9.18	-15.59	-7.10
0.50 mg clemastine	192.87	-19.95	-31.32	-37.21	-43.82	-28.71
1.0 mg clemastine	187.42	-15.17	-34.09	-47.61	-43.23	-32.84

Baseline flare sizes for the 0.5 mg and 1.0 mg doses of clemastine were larger than the 0.25 mg dose and placebo. A dose-related suppression of flare size with a dose response effect was noted for the 0.5 mg and 1.0 mg doses of clemastine. Suppression of flare size was noted for the 0.25 mg dose of clemastine only at 8 hours post-dose. Suppression of flare size was noted for the 0.5 mg dose of clemastine at 6 hours post-dose, and was suggested at 2 and 4 hours post-dose. Peak suppression of flare size for the 0.5 mg dose of clemastine was at 6 hours post-dose. Suppression of flare size was noted for the 1.0 mg dose of clemastine at 2 hours post-dose, and continued until 12 hours post-dose. Peak suppression of flare size for the 1.0 mg dose of clemastine was at 8 hours post-dose. There was a dose response effect at all time points post-dose. These data are displayed in Table 8.3.2.

Table 8.3.2 HSC-303, change from baseline in flare size [Volume 1.23, page 59]

Treatment	Baseline, mm2	Change from baseline, mm2				
	0 hours	2 hours	4 hours	6 hours	8 hours	12 hours
Placebo	1610.30	-123.19	-23.75	-4.17	-118.73	34.41
0.25 mg clemastine	1605.06	-132.49	-104.89	-138.66	-183.79	-106.18
0.50 mg clemastine	1648.19	-195.31	-146.78	-318.26	-275.60	-232.83
1.0 mg clemastine	1732.46	-298.08	-338.60	-528.72	-549.57	-449.14

8.3.4.3. Safety

Safety variables for this study were AEs, vital signs, physical examination, hematology, chemistry, urinalysis, and ECGs [Volume 1.23, page 181].

There were 10 AEs among the 24 subjects. These 10 AEs occurred in four subjects [Volume 1.23, pages 44, 71]. There were seven AEs in patients taking clemastine (29.2%) and three AEs in patients taking placebo (12.5%). AEs occurring in more than one clemastine-treated patient were cough and rhinitis, which occurred in two patients each (8.3%). Cough and rhinitis were not seen in placebo treated patients. These data are displayed in Table 8.3.3. There were no deaths or SAEs in this study. There were no withdrawals from the study because of AEs [Volume 1.23, page 44].

Table 8.3.3 HSC-303, adverse events [Volume 1.23, page 71]

	Clemastine								Placebo	
Adverse Event	All doses N=24		0.25 mg N=24		0.50 N=24		1.00 N=24		N=24	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cough	2	(8.3)	1	(4.2)	1	(4.2)	0	(0)	0	(0)
Rhinitis	2	(8.3)	1	(4.2)	1	(4.2)	0	(0)	0	(0)
Back pain	1	(4.2)	0	(0)	0	(0)	1	(4.2)	0	(0)
Pharyngitis	1	(4.2)	0	(0)	1	(4.2)	0	(0)	0	(0)
Runny nose	1	(4.2)	0	(0)	1	(4.2)	0	(0)	0	(0)
Fatigue	0	(0)	0	(0)	0	(0)	0	(0)	1	(4.2)
Fever	0	(0)	0	(0)	0	(0)	0	(0)	1	(4.2)
Hot flushes	0	(0)	0	(0)	0	(0)	0	(0)	1	(4.2)
All events	7	(29.2)	2	(8.3)	4	(16.7)	1	(4.2)	3	(12.5)

There were no changes in physical examination from baseline [Volume 1.23, page 43]. There was a slight increase in systolic blood pressure of 3 to 7 mm Hg in all treatment groups. The largest increase in systolic blood pressure was 7 mm Hg in the 0.5 mg clemastine group. There was no dose response effect noted. No subject had a post-baseline systolic blood pressure >140 mm Hg [Volume 1.23, page 43, 61]. There were no changes from baseline in the diastolic blood pressure among treatment groups. No subject had a diastolic blood pressure >90 mm Hg [Volume 1.23, page 43, 62]. There was a slight increase in respiratory rate of 1/min to 2.6/min in all treatment groups, including the placebo group. There was no dose response effect noted [Volume 1.23, page 63]. There was a slight increase of pulse of 2 to 7 bpm all treatment groups. There was no dose response effect noted [Volume 1.23, page 64]. All ECGs were normal and there was no change in ECGs during the study [Volume 1.23, page 4].

There were no clinically significant changes in hematology studies [Volume 1.23, pages 6-8]. There were some small changes in chemistry. Two subjects had an increase in CPK to two times normal levels at the end of the study. One patient had an increase of CPK from 141 to 271 U/L and a second subject had an increase of CPK from 134 to 410 U/L. This change is of unclear significance. Eight subjects had an increase in triglycerides. It is possible that this change could be related to the diet administered at the study center. A "standard" breakfast was served after the study treatment was administered with lunch served three hours afterwards. Other meals and times of meals are not noted in the protocol or report [Volume 1.23, pages 6-19, 24]. There were no other notable changes in chemistry. There were no significant changes in urinalysis in any treatment group [Volume 1.23, page 140-142].

8.4. HSC-304: A randomized, single center, double blind, placebo controlled, cross-over study to investigate the efficacy and duration of action of clemastine fumarate 0.67 mg tablet (0.50 mg clemastine) in reducing symptoms and secretions after intranasal antigen challenge in patients with a history of allergic rhinitis.

8.4.1. Summary and reviewer's conclusion of study results

This was to be a double blind, four-period, crossover study, performed in male and female patients ≥18 years of age with SAR. The objective of this study was to evaluate the efficacy of a single dose of 0.5 mg clemastine in decreasing symptoms produced by intranasal challenge with allergen. In addition, suppression of wheal and flare from histamine intradermal skin test was evaluated. The sponsor also sought to determine if the antihistamine effects of 0.5 mg clemastine persist for 6 hours.

The study was designed as a four-period crossover study. However, the randomization schedule was incorrectly done as a three-period crossover design, and for all patients the fourth period was placebo. This potentially could bias the study from a carryover effect to the placebo phase, priming effect, time effect, or other effect. Priming from sequential weekly antigen challenge may have increased the level of sensitivity of patients and possibly could have made it more difficult to demonstrate efficacy. These deficiencies limit the conclusions that can be drawn from this study.

There were multiple primary efficacy variables for this study. They included the number of sneezes and symptom severity after nasal allergen challenge and the change in the size of the wheal and flare responses to histamine skin test. Nasal secretion weight and total albumin in nasal secretions were secondary efficacy variables. Clemastine decreased sneezes, runny nose, and watery eye symptoms when given prior to nasal allergen challenge. There was no decrease in stuffy nose when clemastine was administered prior to nasal allergen challenge. There was a suggestion of a decrease in itchy nose/throat and itchy eye symptoms with administration of clemastine prior to nasal allergen challenge. Clemastine decreased the Total Signs and Symptoms score when given prior to nasal allergen challenge. The drug effect on each of the clinical symptoms was present when clemastine was administered up to 6 hours prior to challenge. Clemastine did not suppress wheal size, but there was a suggestion of suppression of flare size after histamine skin test. This lack of wheal suppression is unlikely

to be due to drug effect, since there were concomitant decreased symptoms and flare size suppression. Clemastine decreased nasal secretion weights but did not decrease total albumin in nasal secretions.

In addition to deficiencies from the study design noted above, it should be noted that there is little clinical relevance with nasal allergen challenge and histamine skin test suppression as models of allergic disease. Acute challenge with allergen extract is not a natural method of exposure and has an unclear correlation with clinical response in SAR. In addition, histamine release is only a component of the allergic response. As such, these models cannot be accepted as surrogates for the study of the clinical response to an antihistamine.

Safety variables for this study included AEs, vital signs, physical examination, hematology, chemistry, and urinalysis. ECGs were not performed in this study. There were 10 AEs among the 21 clemastine treated patients in this study (47.6%). There were two AEs in 20 placebo-treated patients (10.0%). The only AE occurring in more than one clemastine-treated patient was URI, which occurred in four patients (19.0%). URI was not seen in placebo treated patients. There were no deaths or SAEs in this study and no patients withdrew from the study because of AEs. There were no drug-related changes in physical examination from baseline in this study. There were no clinically significant changes in vital signs, hematology studies, or urinalyses. There were some small changes in chemistry. Three patients had a small increase in CPK at the end of the study. These patients' CPKs returned to normal with a follow-up sample. One patient had an elevation of triglyceride that returned to normal in a follow-up sample. There were no other notable changes in chemistry. This study supports the safety of clemastine.

8.4.2. Objective

The objective of this study was to evaluate the efficacy single dose of 0.5 mg clemastine in the suppression of symptoms produced by intranasal challenge with allergen. In addition, suppression of wheal and flare from histamine intradermal skin test was evaluated. The sponsor also sought to determine if the antihistamine effects of 0.5 mg clemastine persist for 6 hours [Volume 1.24, pages 18, 181].

8.4.3. Protocol

This study was designed as a four-period crossover study, but was mistakenly conducted as a three-period crossover design [Volume 1.24, pages 27, 182], with the fourth period being placebo for all patients as shown in Table 8.4.1.a. Patients were randomized to one of six treatment sequences (A-F), depending on the timing (T1, T4, T6) of clemastine 0.5 mg or placebo dosing prior to nasal allergen challenge and histamine skin test (Tables 8.4.1.a. and 8.4.1.b.).

Table 8.4.1.a Treatment sequences, HSC-304

Treatment sequence	Period 1*	Period 2	Period 3	Period 4
A	T6**	T4	T1	P
B	T4	T6	T1	P
C	T1	T6	T4	P
D	T6	T1	T4	P
E	T1	T4	T6	P
F	T4	T1	T6	P

*Washout period was 14 days between periods.
**T6, T4, T,1, and P are defined in Table 8.4.1.b.

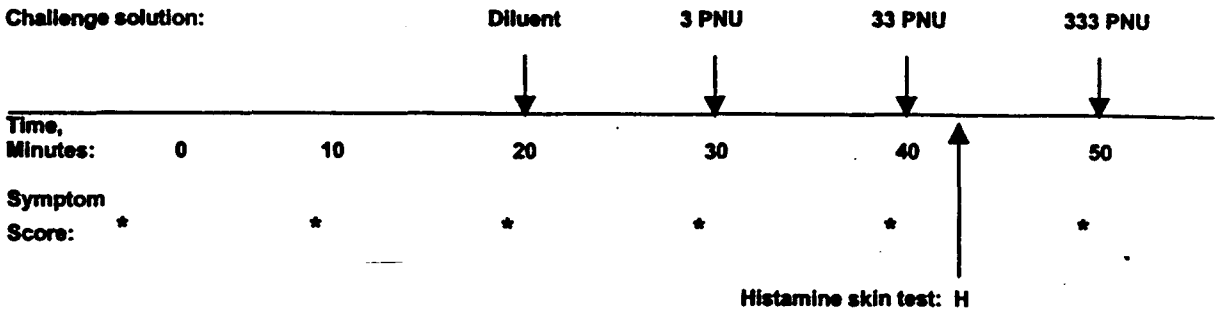
Table 8.4.1.b Challenge schedules, HSC-304

	Treatment and time before allergen challenge and histamine skin test			
Challenge day schedule	-6 hours	-4 hours	-1 hour	0 hours
T6	Clemastine 0.5 mg	Placebo	Placebo	Nasal allergen challenge and histamine skin test
T4	Placebo	Clemastine 0.5 mg	Placebo	Nasal allergen challenge and histamine skin test
T1	Placebo	Placebo	Clemastine 0.5 mg	Nasal allergen challenge and histamine skin test
P	Placebo	Placebo	Placebo	Nasal allergen challenge and histamine skin test

Patients were screened up to six months and no less than two weeks prior to the start of the study. Patients were males or females at least 18 years of age who had a history of allergic rhinitis and were skin test sensitive to either grass or ragweed pollen. Patients must have demonstrated reproducible positive responses to nasal allergen challenge. (The nasal allergen challenge procedure is described in the following paragraph). A positive response to nasal allergen challenge was defined as a two-fold increase over the diluent response in two of the following symptoms: sneezing, rhinorrhea (secretion weight), or level of albumin in nasal secretions in response to one of three allergen doses. Patients also must have at least a two-fold increase in the largest wheal and flare diameter over the diluent control with intradermal skin test with [redacted] mg/ml of histamine [Volume 1.24, page 183]. Medication batches used in this study were clemastine 0.5 mg tablets, 651-1890.36, and placebo, 651-1927.01 [Volume 1.24, page 31].

The nasal allergen challenge procedure follows. Pre-weighed filter paper discs were applied to the anterior portion of the nasal septum and weighed after application. Baseline measurements of nasal secretions were taken prior to and after saline nasal lavage. Lavage fluid was measured for total albumin content. Challenges with diluent control, 3 PNU, 33 PNU, and 333 PNU of allergen were performed sequentially at 10 minute intervals. Challenge was performed by applying diluent control or allergen to a filter paper disc. The disc was placed on the anterior nasal septum. The diluent or allergen disc was allowed to remain in place for one minute before removal. After removal of the diluent or allergen disc, dry discs were applied to the anterior nasal septum to collect secretions after 30, 60, and 90 seconds. Discs were weighed to assess the amount of rhinorrhea and were eluted to measure albumin levels as an measure of extravasation [Volume 1.24, page 191]. Symptom evaluations were performed prior to the baseline evaluation, at the end of the diluent control challenge, and after nasal allergen challenge. The following symptoms were rated in severity by the patient: runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes. Symptoms were rated on a four point scale, where 0=not present, 1=mild, 2=moderate, and 3=severe. The nasal allergen challenge schedule is displayed in Figure 8.4.1.

Figure 8.4.1. Nasal challenge with allergen, HSC-304



Histamine skin test was performed on the volar surface of the forearm with saline control solution and — mg/mL and — mg/mL of histamine phosphate. Histamine skin test was performed after the 33 PNU nasal challenge and before the 333 PNU nasal challenge. Skin test responses were measured at 10 minutes. Reaction size was measured by measuring the wheal or flare diameter in two perpendicular directions and halving the sum [Volume 1.24, page 192].

There were multiple primary efficacy variables for this study. They included the number of sneezes and symptom severity after nasal allergen challenge and the change in the size of the wheal and flare responses to histamine skin test. Nasal secretion weight and total albumin in secretions were secondary efficacy variables [Volume 1.24, page 34]. Safety variables for this study included AEs, vital signs, physical examination, hematology, chemistry, and urinalysis. ECGs were not performed in this study [Volume 1.24, page 279].

8.4.4. Results

8.4.4.1. Demographics, Protocol Violations

Thirty-eight patients were screened and 21 were enrolled. The study was designed as a 4-period crossover study. However, the randomization schedule was incorrectly done as a 3-period crossover design, and for all patients the fourth period was placebo [Volume 1.24, pages 27, 182]. This potentially could bias the study from a carryover effect to the placebo phase, priming effect, time effect, or other effect. Priming from sequential weekly antigen challenge may have increased the level of sensitivity of patients and possibly could have made it more difficult to demonstrate efficacy. These deficiencies limit the conclusions that can be drawn from the efficacy results of this study.

Twenty patients completed the study. One patient withdrew his consent after the first treatment period. He was included in the safety analysis but not the efficacy analysis [Volume 1.24, page 36]. The average age for patients was 25.5 years with a range of 18-36 years. There were 16 male patients (76%, 16/21) and 5 female patients (24%, 5/21). There were 15 Caucasian patients (71%, 15/21), two Black patients (10%, 2/21), three Oriental patients (14%, 3/21), and one with race not specified (5%, 1/21) [Volume 1.24, pages 51-52]. Baseline laboratory values for SGPT, CPK, and triglycerides were omitted in error in

approximately 50% of patients. There were no other protocol violations [Volume 1.24, page 37].

8.4.4.2. Efficacy variable outcomes

Clemastine decreased sneezes, runny nose, and watery eye symptoms when administered at 1, 4, and 6 hours prior to nasal allergen challenge. Clemastine did not decrease stuffy nose symptoms when administered prior to nasal allergen challenge. There was a suggestion that clemastine decreased itchy nose/throat and itchy eye symptoms when administered at 1, 4, and 6 hours prior to challenge with the highest dose of allergen. Clemastine decreased the Total Signs and Symptoms score, a post-hoc variable, when given at 1, 4, and 6 hours prior to nasal allergen challenge. Clemastine did not suppress wheal size induced by histamine skin test. There was a suggestion that clemastine suppressed flare induced by histamine skin test. Secondary efficacy endpoints included nasal secretion weight and total albumin in nasal secretions after nasal allergen challenge. Clemastine decreased nasal secretion weights when given 4 and 6 hours prior to challenge. Clemastine did not affect total albumin in nasal secretions when given prior to challenge. Efficacy variables are described in detail below. As noted previously in this review, there were multiple primary variables for this study. Accordingly, this review will not present statistical tests of significance, but will present the results in a descriptive fashion.

Clemastine decreased sneezes from the 33 PNU and 333 PNU doses of allergen when given at 1, 4, and 6 hours prior to nasal allergen challenge. There was little decrease in sneezes at any time point noted with diluent challenge and the 3 PNU dose. These data are displayed in Table 8.4.2.

Table 8.4.2 Sneezing, intranasal allergen challenge, HSC-304 [Volume 1.24, page 39]

		Ragweed or grass pollen allergen		
Treatment	Diluent	3 PNU	33 PNU	333 PNU
P	0.5	0.5	3.0	4.8
T1	0.2	0.6	1.6	3.3
T4	0.1	0.1	1.7	1.8
T6	0.0	0.0	1.0	2.2

T1: Clemastine 0.5 mg given 1 hour before challenge, placebo at 4 and 6 hours before challenge
T4: Clemastine 0.5 mg given 4 hours before challenge, placebo at 1 and 6 hours before challenge
T6: Clemastine 0.5 mg given 6 hours before challenge, placebo at 1 and 4 hours before challenge
P: Placebo given at 1, 4, and 6 hours prior to challenge

Clemastine slightly decreased runny nose and watery eye symptoms from the 33 PNU and 333 PNU doses of allergen when given 1, 4, and 6 hours prior to nasal allergen challenge. Clemastine produced little decrease in runny nose and watery eye symptoms when given before the 3 PNU dose of allergen or diluent challenge [Volume 1.24, pages 41, 43].

Clemastine did not decrease stuffy nose symptoms when given before 3, 33, and 333 PNU doses of allergen or diluent [Volume 1.24, page 41].

Clemastine did not decrease itchy nose/throat and itchy eye symptoms when given before the 3 or 33 PNU doses of allergen. There was a suggestion that clemastine decreased itchy nose/throat and itchy eye symptoms when given at 1, 4, and 6 hours prior to nasal allergen challenge with the 333 PNU dose of allergen [Volume 1.24, page 42].

The study report gives the results of a post-hoc variable, the Total Signs and Symptoms score. This variable was the sum of symptom scores for runny nose, stuffy nose, itchy nose or throat, itchy eyes, and watery eyes. Clemastine decreased the Total Signs and Symptoms score when given 1, 4, and 6 hours prior to nasal allergen challenge with the 33 PNU and 333 PNU doses of allergen. Clemastine produced little decrease in Total Signs and Symptoms score at any time point when given before the 3 PNU dose of allergen and diluent challenge [Volume 1.24, page 43].

Clemastine was given 1, 4, and 6 hours prior to skin testing with ——— mg/mL of histamine. Clemastine produced no suppression of wheal size when given before skin test before either dose of histamine. These data are presented in Table 8.4.3.

Table 8.4.3 Histamine skin test suppression, wheal size [Volume 1.24, page 38]

Treatment	Diluent	Histamine, — mg/mL	Histamine, — mg/ml
P	3.78	7.30	9.95
T1	3.30	7.30	10.78
T4	3.40	7.66	10.93
T6	2.90	7.15	10.20

T1: Clemastine 0.5 mg given 1 hour before challenge, placebo at 4 and 6 hours before challenge
T4: Clemastine 0.5 mg given 4 hours before challenge, placebo at 1 and 6 hours before challenge
T6: Clemastine 0.5 mg given 6 hours before challenge, placebo at 1 and 4 hours before challenge
P: Placebo given at 1, 4, and 6 hours prior to challenge

There was a suggestion that clemastine suppressed flare when given before skin testing with the lower dose of histamine. The absolute effect size was small, however, and was not present with the higher dose of histamine. These data are displayed in Table 8.4.4.

Table 8.4.4 Histamine skin test suppression, flare size [Volume 1.24, page 39]

Treatment	Diluent	Histamine, — mg/mL	Histamine, — mg/ml
P	0.48	12.85	33.33
T1	0.40	13.15	33.38
T4	0.75	11.10	33.53
T6	0.50	9.08	29.90

T1: Clemastine 0.5 mg given 1 hour before challenge, placebo at 4 and 6 hours before challenge
T4: Clemastine 0.5 mg given 4 hours before challenge, placebo at 1 and 6 hours before challenge
T6: Clemastine 0.5 mg given 6 hours before challenge, placebo at 1 and 4 hours before challenge
P: Placebo given at 1, 4, and 6 hours prior to challenge

The lack of wheal suppression is unlikely to be due to drug effect, since there were concomitant decreased symptoms and that flare size suppression.

Secondary efficacy endpoints include nasal secretion weight and total albumin in nasal secretions after nasal allergen challenge. Clemastine decreased nasal secretion weights when given 4 and 6 hours prior to challenge with the 33 and 333 PNU doses of allergen. There was no effect noted with diluent and 3 PNU doses of allergen [Volume 1.24, page 40]. There was little change in total albumin in nasal secretions with drug with any dose of allergen [Volume 1.24, page 40].

8.4.4.3. Safety

Safety variables for this study were AEs, vital signs, physical examination, hematology, chemistry, and urinalysis [Volume 1.24, page 279].

There were 10 AEs among the 21 clemastine-treated patients in this study (47.6%) [Volume 1.24, pages 44]. These 10 AEs occurred in eight patients. There were two AEs in 20 placebo-treated patients (10.0%, 2/20). The only AE occurring in more than one clemastine-treated patient was URI, which occurred in four patients (19.0%, 4/21). URI was not seen in placebo treated patients. These data are displayed in Table 8.4.4. Review of AEs reveals that there were no deaths or SAEs in this study and no patients withdrew from the study because of AEs [Volume 1.24, page 44].

Table 8.4.4 HSC-304, adverse events [Volume 1.24, page]

Adverse Event	Clemastine N=21		Placebo N=20	
	n	(%)	n	(%)
URI	4	(19.0)	0	(0)
Sunburn	1	(4.8)	0	(0)
Migraine headache	1	(4.8)	0	(0)
Lightheadedness	1	(4.8)	0	(0)
Jittery feeling	1	(4.8)	0	(0)
Dry mouth	1	(4.8)	0	(0)
Ankle sprain	1	(4.8)	0	(0)
Fatigue	0	(0)	1	(5.0)
Headache	0	(0)	1	(5.0)
All events	10	(47.6)	2	(10.0)

Two patients had changes in physical examination from baseline in this study. One patient developed a sunburn and another experienced a sprained ankle [Volume 1.24, page 43]. In this reviewer's opinion, neither are likely to be drug-related.

There were no clinically significant changes in vital signs. There was a small, clinically insignificant increase in mean respiratory rate of 1.1/min from a baseline of 17.1/minute overall. [Volume 1.24, pages 44, 69-73].

There were no clinically significant changes in hematology studies or urinalyses [Volume 1.24, pages 4-5, 8, 44]. There were some small changes in chemistry. Three patients had a small increase in CPK at the end of the study. One patient had increase of CPK from 63 IU/L to 617 IU/L and another from 86 IU/L to 744 IU/L. These patients' CPKs returned to normal at a follow-up sample. One patient did not have a baseline CPK and had a minimally elevated CPK of 240 IU/L at close of study [Volume 1.24, pages 6-7, 161-163]. These changes are of unclear significance. One patient had an elevation of triglycerides from 138 mg/dL to 375 mg/dL. This patient's triglycerides returned to 195 mg/dL in a follow-up specimen [Volume 1.24, page 164]. There were no other notable changes in chemistry [Volume 1.24, pages 6-7, 161-166].

8.5. PK Studies: HSC-151, HSC-152, HSC-153B, HSC-302

There were four PK studies included in this application. These four PK studies included three single dose PK studies and one multiple dose PK study. A summary of the PK studies is presented in Table 8.5.1.

Table 8.5.1 Summary of pharmacokinetics studies, NDA 21-082

Study Number	Treatment Groups	Duration of treatment	Design	Number of subjects
[redacted]				
HSC-151	1 clemastine tab 0.5 mg QID 1 clemastine tab 1 mg BID	7 days each period	2 period crossover	22
HSC-152	2 CTC tabs 1 clemastine tab 0.5 mg clemastine syrup 0.5mg 2 Thera-Flu® tabs	Single dose 7 day washout	4 way crossover	32
HSC-153B	4 CTC tabs 2 clemastine tabs 0.5 mg 2 clemastine tabs 0.5 mg plus 4 Thera-Flu® tabs 1 clemastine tab 1.0 mg (Tavist-1®)	Single dose 7 day washout	4 way crossover	32
HSC-302	1 clemastine tab 0.5 mg 1 clemastine 1 mg	Single dose	2 period crossover	22

The sponsor's conclusions from these studies are summarized below [Volume 1.1, page 61]:

- Multiple dosing with 0.5 mg clemastine tablets QID is bioequivalent to multiple dosing with Tavist-1® (1.0 mg clemastine) BID.
- Single doses of four CTC tablets, two 0.5 mg clemastine tablets, and one Tavist-1® tablet are bioequivalent.
- The presence of acetaminophen and pseudoephedrine and the CTC formulation in which clemastine, acetaminophen, and pseudoephedrine were combined does not affect the pharmacokinetics of clemastine.
- The addition of clemastine to acetaminophen and pseudoephedrine does not affect the pharmacokinetics of acetaminophen and pseudoephedrine.
- The CTC formulation in which clemastine, acetaminophen, and pseudoephedrine are combined does not affect the pharmacokinetics of acetaminophen and pseudoephedrine.

More detail on the PK findings from these studies may be found in Dr. Wakelkamp-Barnes' biopharmacology review.

There were 54 patients exposed to 1.0 mg clemastine and 86 patients exposed to 0.5 mg clemastine in single dose PK studies. AEs noted in the PK studies were generally mild to moderate in severity and did not reveal any new safety signal for clemastine. There were no SAEs or deaths. There were two withdrawals due to AEs in clemastine-treated patients, one patient with itching, rash, nausea, and pallor and another with vomiting. Nausea, rash, and vomiting have been reported with clemastine and other antihistamines. There were two subjects with clinically significant elevation in BP. There were no other clinically significant changes in vital signs. There were no clinically significant changes from normal to abnormal in physical examination. Five subjects developed increased CPK levels. This reviewer searched Medline and AERS and did not find reports of elevated CPK in clemastine-treated patients. There were no clinically significant changes in ECGs. Otherwise, these data do not reveal any new safety signal for clemastine.

A summary of PK results and review of safety findings of these studies follow.

8.5.1. PK study results

The PK findings of these studies will be briefly summarized. Please refer to Dr. Wakelkamp-Barnes' biopharmacology review for a detailed discussion of PK results.

The objective of HSC-151 was to assess the steady-state pharmacokinetic bioavailability parameters of two different dosage regimens of clemastine (0.5 mg QID vs. 1.0 mg BID) in healthy male subjects. HSC-151 was an open label, two-way crossover study in 22 healthy males, 7 days each period, with a total duration of 17 days. This study showed that dosing with 0.5 mg clemastine tablets QID was bioequivalent to dosing with Tavist-1® tablets BID. There was no drug accumulation with dosing of clemastine 0.5 mg QID [Volume 1.1, pages 44, 49-52].

The objectives of HSC-152 were to assess the pharmacokinetic interaction of clemastine, acetaminophen, and pseudoephedrine and to determine the bioequivalence of clemastine administered as a 0.5 mg tablet and as the CTC tablet in healthy male and female subjects. HSC-152 was an open label, four-way crossover study comparing two CTC tablets, one 0.5 mg clemastine tablet, 5 ml Tavist® syrup (0.5 mg clemastine), and two Thera-Flu® Sinus tablets (TF Sinus, acetaminophen 500 mg plus pseudoephedrine 30 mg). There were 32 healthy male and female subjects. This study showed that CTC tablets and TF Sinus tablets were bioequivalent with respect to acetaminophen and pseudoephedrine and that clemastine did not affect the bioavailability of either acetaminophen or pseudoephedrine. CTC tablets were not bioequivalent to either the clemastine 0.5 mg tablet or Tavist® syrup with respect to clemastine. C_{max} was 570.2 pg/ml for clemastine dosed as two CTC tablets. AUC_{0-t} was 7273.6 pg/h/mL and AUC_{0-inf} was 9798.7 pg/h/mL and T_{max} was 6 hours. [Volume 1.1, pages 44, 52-53].

The objectives of HSC-153B were to investigate the bioavailablity of clemastine, acetaminophen, and pseudoephedrine, to assess drug interaction, and to link clemastine in the CTC product to the 0.5 mg clemastine tablet and a currently marketed formulation of clemastine. HSC-153B was an open label, four-way crossover study. There were 32 male subjects. This study showed that CTC tablets and 0.5 mg clemastine tablets administered with TF Sinus tablets were bioequivalent with respect to both acetaminophen and pseudoephedrine. C_{max} was 1005.3 pg/mL for clemastine dosed as four CTC tablets. AUC_{0-t} was 18732.2 pg/h/mL and AUC_{0-inf} was 23155.8 pg/h/mL for clemastine [Volume 1.1, page 44, 57-60].

The objective of HSC-302 was to determine the bioavailability and dose proportionality of single doses of 0.5 mg and 1.0 mg clemastine in healthy male subjects. HSC-302 was two period crossover, single dose study performed on 2 separate days. There was a 7-day washout. There were 22 healthy male subjects. This study found that the 1.0 mg clemastine tablets and Tavist-1® (clemastine 1.0 mg) tablets were not bioequivalent, and there was no dose-proportionality between single doses of 0.5 mg and 1.0 mg clemastine [Volume 1.1, pages 44, 48-49].

8.5.2. Safety

Safety findings will be discussed in an integrated fashion because of the small numbers of subjects participating in these studies. AEs, SAEs and deaths, withdrawals, vital signs, physical examination, laboratory studies, and ECGs were safety endpoints for these studies. Acetaminophen and pseudoephedrine are monograph antihistamines and are proposed at monograph doses in the CTC product. Clemastine is not a monograph antihistamine and the 0.5 mg QID dose is different than that currently approved. Therefore, the focus of the safety review will be on clemastine and not on acetaminophen or pseudoephedrine. Review of the safety outcomes from the PK studies follows.

8.5.2.1. Exposure

A total of 108 patients were exposed to clemastine in all PK studies. There were 54 patients exposed to 1.0 mg clemastine and 86 patients exposed to 0.5 mg clemastine in single dose PK studies. Patients were exposed to clemastine in the form of the CTC tablet, 0.5 mg and 1.0 mg clemastine tablets, and clemastine syrup. There were 22 subjects exposed to 0.5 mg and 1.0 mg doses of clemastine in one 7-day multiple dose crossover PK study. Patients were exposed to clemastine in the form of the 0.5 mg and 1.0 mg tablets in this study. [Volume 1.9, pages 49, 75, Volume 1.13, pages 35-36, 52-53, Volume 1.17, pages 14, 60, Volume 1.11, pages 15-16, 38]

Subjects ages 19 to 50 years were exposed in single dose PK studies and ages 19 to 49 years in the multiple dose PK study [Volume 1.9, pages 49-75, Volume 1.11, pages 15-16, 38, Volume 1.13, pages 35-36, 52, Volume 1.17, page 60].

There were 70 males and 16 females exposed to clemastine in single dose PK studies. There were 22 males and 0 females exposed to clemastine in the multiple dose PK study [Volume 1.9, pages 49-75, Volume 1.11, page 38, Volume 1.13, pages 35-36, 52, Volume 1.13, page 14].

8.5.2.2. AEs

AEs noted in the PK studies were generally mild to moderate in severity. Notable AEs in clemastine-exposed subjects included rhinitis (24%, 26/108), headache (22%, 24/108), pharyngitis or sore throat (18%, 20/108), fatigue (18%, 19/108), asthenia (12%, 13/108), nausea (10%, 11/108), dizziness (8%, 9/108) and drowsiness (7%, 8/108). Headache, nausea, fatigue, asthenia, dizziness, and drowsiness are recognized adverse events associated with clemastine and other sedating antihistamines [Volume 1.9, pages 133-134, Volume 1.11, pages 112-114, Volume 1.13, pages 84-86, Volume 1.17, pages 52-53, 130, Mosby's Gen Rx™ - 10th Ed. (2000): Clemastine fumarate]. These AEs do not reveal any new safety signal for clemastine.

8.5.2.3. SAEs and deaths

There were no SAEs or deaths in any of the PK studies [Volume 1.34, page 46].

8.5.2.4. Withdrawals

There were two withdrawals due to AEs in clemastine-treated patients in the PK studies. They were Subject 19 in HSC-152 who had itching, rash, nausea, and pallor and Subject 7 in HSC-153B who had vomiting 10 minutes after dosing. Nausea, rash, and vomiting have been reported with clemastine and other antihistamines. There were no other withdrawals in clemastine-treated subjects in the PK studies [Volume 1.13, page 45, Volume 1.17, page 53]. These data do not reveal any new safety signal for clemastine.

8.5.2.5. Vital signs

There were two subjects with clinically significant changes in vital signs in the PK studies. Subject 19 in HSC-302 had an increase in BP while taking clemastine 0.5 mg and 1.0 mg. The BP increased to a maximum of 189/127 mm Hg from a baseline of 148/88 mm Hg. There was no follow-up BP performed. While taking clemastine 1.0 mg, Subject 2 in HSC-153B had a BP that increased to 152/103 mm Hg at close of study from 109/74 mm Hg at baseline. The BP decreased to 138/93 mm Hg with follow-up. [Volume 1.9, page 105, Volume 1.18, page 215]. There were no other clinically significant changes in vital signs in PK studies [Volume 1.9, page 60, Volume 1.11, pages 33-34, Volume 1.13, page 42, Volume 1.17, page 50-51]. Elevated BP has not been associated with clemastine, but clemastine has a long marketing history in this country. These BP changes are not likely to represent a new safety signal.

8.5.2.6. Physical examination

There was three clemastine-treated subjects with a change in physical examination from normal to abnormal in the PK studies. Subject 19 in study HSC-152 developed a painful tooth, mild epigastric tenderness and a rash on both wrists [Volume 1.13, page 42]. There was one patient with impacted cerumen and on patient with a URI in study HSC-151 [Volume 1.11, page 34, 67]. There were no other changes in PE in the other PK studies [Volume 1.9, page 77-98, Volume 1.17, page 50]. These changes in physical examination are not likely to be related to clemastine and do not represent a new safety signal.

8.5.2.7. Laboratory studies

Five subjects developed increased CPK levels in the PK studies. Subject 16 in study HSC-302 had an increase in CPK from 85 IU/L at baseline to 1223 IU/L at the end of the study. There was no follow-up performed [Volume 1.9, page 124]. Subject 8 in study HSC-151 had an increase in CPK from 177 IU/L at baseline to 1700 IU/L at the end of the study. The CPK decreased to normal at follow-up [Volume 1.11, pages 34, 84]. Three subjects in HSC-153B developed elevated CPK levels. Subject 15 had an increase in CPK from 217 IU/L to 392 IU/L. The CPK decreased to 283 IU/L at follow-up. Subject 21 had an increase in CPK from 181 IU/L -239 IU/L. There was no follow-up. Patient 26 had an increase in CPK from 175 IU/L to 273 IU/L at the end of the study. The CPK decreased to 182 IU/L at follow-up [Volume 1.18, pages 199-202]. The elevation in CPK seen in these studies are interesting. This reviewer searched Medline and AERS and did not find reports of elevated CPK in clemastine-treated patients. It may be of benefit to follow future AE reports for additional instances of BP elevation.

Two patients in the PK studies developed a decreased hematocrit. They were both women and both were in HSC-152, Subject 29 had a decrease in hematocrit from 33.9 to 29.4 during the study. The hematocrit increased to 33.5 at follow-up. Subject 23 had a decrease in hematocrit from 39.7 to 28.9 during the study. There was no follow-up sample taken [Volume 1.13, page 43]. These isolated hematocrit changes are not likely to represent a new safety signal.

8.5.2.8. ECGs

There were no clinically significant changes in ECGs during the PK studies. ECGs were done at screening only in HSC-302. There was a decrease in the mean QTc of 10.2 msec in study HSC-153B [Volume 1.17, pages 51, 253-262]. Two patients in HSC-152 had slight elevations in QT at the end of the study. Subject 1 had a QT of 408 msec that increased to 451 msec. The QTc in this patient was 411 msec at beginning and 411 msec at the end of the study. Subject 7 had a QT of 405 msec that increased to 445 msec at the end of the study. The QTc in this subject decreased from 394 msec at baseline to 389 msec at the end of the study [Volume 1.13, page 43, 121-122]. These ECG changes do not represent a new safety signal.

9. OVERVIEW OF EFFICACY

Clemastine is currently approved as an OTC product for the temporary reduction of runny nose and sneezing due to hay fever, other respiratory allergies, or the common cold at the dose of 1 mg twice daily. It is not approved for [redacted]
It is also indicated for temporary reduction of nose or throat itching and itchy, watery eyes due to hay fever or other upper respiratory allergies. The proposed dose of clemastine in the CTC product is 0.5 mg every 6 hours, a dose for which efficacy has not been established. Acetaminophen and pseudoephedrine are cough and cold OTC monograph drugs. The dose and dosing intervals of acetaminophen and pseudoephedrine in the CTC product are the same as those listed in the OTC monograph, and the sponsor is not required to demonstrate efficacy of these two drugs in the CTC combination.

Therefore, the main requirements of the sponsor's clinical development program for CTC were to show the efficacy of clemastine 0.5 mg every 6 hours for the treatment of the symptoms of allergic rhinitis, that efficacy is maintained until the end of the 6 hour dosing interval, that efficacy is maintained in the combination product, and that clemastine in the CTC product adds benefit to the combination of acetaminophen and pseudoephedrine. The sponsor has submitted two pivotal clinical studies HSC-305 and HSC-306 to meet these requirements.

These two pivotal clinical studies demonstrate the efficacy of the CTC product in the treatment of symptoms of seasonal allergic rhinitis. HSC-305 showed that clemastine 0.5 mg every 6 hours was superior to placebo in the treatment of the symptoms of seasonal allergic rhinitis. Primary efficacy variables were physician- and patient-assessed rhinorrhea and sneezing scores. Clemastine 0.5 mg every 6 hours produced maximum effect sizes for the primary efficacy variables of approximately 6%-14%. The patient-assessed instantaneous individual treatment score, a secondary efficacy variable, showed that efficacy was maintained to the end of the dosing interval for clemastine 0.5 mg every 6 hours.

HSC-306 showed that CTC was superior to TF Sinus and placebo for the primary efficacy variable, the Major Symptom Complex (MSC). The MSC was the sum of individual scores for sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. The effect size for CTC was 5%-8% compared with TF Sinus and placebo. This study also showed that the CTC combination product is superior to the combination of acetaminophen and pseudoephedrine alone in the treatment of the symptoms of seasonal allergic rhinitis. Results of secondary efficacy variables also support the efficacy of CTC. This study showed that the onset of efficacy of the CTC product was at 2 hours and that efficacy was maintained throughout the 6 hour dosing interval. These studies are summarized in greater detail below.

HSC-305 was a two-week, multi-center, double-blind, double-dummy, placebo-controlled, randomized, parallel-group, Phase 3 study that was performed in 12 U.S. centers. HSC-305 supports the efficacy of clemastine 0.5 mg every 6 hours for the treatment of symptoms and signs of SAR. The primary efficacy variables were not clearly defined. This reviewer considered the physician-assessed rhinorrhea and sneezing scores and patient-assessed instantaneous and reflective rhinorrhea and sneezing scores to be primary efficacy variables. Clemastine 0.5 mg QID and clemastine 1.0 mg BID were superior to placebo for all primary efficacy variables at Visits 2 (Day 4) and 3 (Day 8), and for some at Visit 4 (Day 15). Clemastine 0.5 mg every 6 hours produced maximum effect sizes for the primary efficacy variables of approximately 6%-14%. These data are displayed in Table 9.1. An improvement was seen in the placebo group at Visit 4 compared with baseline. This improvement in the placebo group may represent a placebo effect, or may reflect decrease in patient symptoms due to the lower pollen counts present at the end of the study. This improvement in the placebo group resulted in the lack of difference in the change from baseline at Visit 4 between active drug and placebo groups in most of the primary efficacy variables. Results of secondary efficacy variables support the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID. The patient-assessed instantaneous individual treatment scores show that efficacy is maintained to the end of the dosing interval for both treatment regimens.

Table 9.1 Effect size* for primary efficacy variables, HSC 305.**

Variable	Day 4 (Visit 2) Effect Size	Day 8 (Visit 3) Effect Size	Day 15 (Visit 4) Effect Size
Investigator-assessed rhinorrhea score	11.2%	6.0%	1.3%
Investigator-assessed sneezing score	14.2%	10.0%	5.1%
Patient-assessed rhinorrhea score, instantaneous	7.4%	5.7%	1.3%
Patient-assessed rhinorrhea score, reflective	8.7%	7.4%	3.7%
Patient-assessed sneezing score, instantaneous	9.0%	7.6%	5.0%
Patient-assessed sneezing score, reflective	10.9%	11.0%	9.7%

* Effect size calculated as:

$$\text{Effect Size} = \frac{\text{(change from baseline in symptom score, clemastine 0.5 mg Q6H) - (change from baseline in symptom score, placebo)} \times 100}{\text{Maximum possible change=7}}$$

**Compiled from Tables 8.1.9.-8.1.14. of this review.

HSC-306 was a one-day, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study was performed at two US centers. HSC-306 supports the efficacy of CTC in the treatment of the symptoms of SAR. The primary efficacy variable was the average reduction from baseline in the Major Symptom Complex (MSC) at hours 2-5.

The MSC was composed of the sum of individual scores for sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. The primary comparison was CTC versus TF Sinus, to assess whether any efficacy is added by clemastine in the combination product. CTC decreased MSC scores over hours 2-5 more than TF Sinus and placebo after both doses of treatment medication. The effect size for CTC after Dose 1 was 5.2% of the maximum possible MSC of 33 and the effect size for CTC after Dose 2 was 7.2% of the maximum possible MSC of 33 when compared with TF Sinus. These data are displayed in Table 9.2. There was a placebo effect noted after both doses. Results of secondary efficacy variables also support the efficacy of CTC. Onset of efficacy was at 2 hours and efficacy was maintained throughout the 6 hour dosing interval.

Table 9.2 Effect size* for primary efficacy variables, HSC 306.**

Variable	Time Point	CTC vs. TF Sinus	CTC vs. Placebo
		Effect size, %	Effect size, %
MSC score, hours 2-5	Hour 6 (Dose 1)	5.2	5.2
MSC score, hours 2-5	Hour 12 (Dose 2)	7.2	8.2

*Effect size calculated as:

$$\text{Effect Size} = \frac{\text{(change from baseline in MSC score, CTC) minus (change from baseline in MSC score, placebo or TF Sinus) X 100}}{\text{Maximum possible change=33}}$$

**Compiled from Table 8.2.9 of this review

10. OVERVIEW OF SAFETY

10.1. Summary

Safety data from pivotal controlled clinical studies, PD and PK studies, data from the Agency's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS), and the sponsor's review of the published literature were examined to provide this overview of safety. Treatment exposure in the clinical development program for CTC was adequate to assess safety. Somnolence, fatigue, dry mouth, dyspepsia, abdominal pain, and nausea were identified as common AEs. These AEs have previously been noted with clemastine and other first generation antihistamines and represent no new safety signal. There were no SAEs or deaths in any of the clinical studies. Elevated BP and elevated CPK were seen in patients taking clemastine in these clinical trials. There were no ECG changes noted in any of the clinical studies. Review of AEs, SAEs, deaths, and overdose reports from the Agency's SRS database identified elevated BP as a possible safety signal. Review of the SRS and AERS databases and review of the sponsor's literature survey identify no new safety concerns for clemastine.

10.2. Content

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

- Safety data from the following studies
  - Pivotal controlled clinical studies HSC-305 and HSC-306
  - PD studies HSC-303 and HSC-304
  - PK studies HSC-151, HSC-152, HSC-153B, and HSC-302

- The sponsor's summary and listings of AEs, SAEs, deaths, and overdoses identified by the Agency's Spontaneous Reporting System (SRS) database
- The sponsor's listing of congenital anomalies identified by the Agency's Spontaneous Reporting System (SRS) database and congenital anomalies from the Agency's Adverse Event Reporting System (AERS) database identified by this medical reviewer.
- The sponsor's review of the clinical literature for articles related to the safety of clemastine

10.3. PK, PD, and pivotal controlled clinical studies

Review of safety data from the PK, PD, and pivotal controlled clinical studies included in this application follow.

10.3.1. Exposure

Patients were exposed to multiple dose forms of clemastine in the drug development program for CTC. These dose forms included clemastine syrup, 0.5 mg and 1.0 mg tablets, and the CTC product. In addition, patients were exposed to acetaminophen and pseudoephedrine in the form of TheraFlu® Sinus in study HSC-306. Treatment exposure in the clinical trials for development of CTC is displayed in Table 10.3.1.

Patients were exposed to clemastine in five single dose studies. These were HSC-302, HSC-151, HSC-153B, HSC-303, and HSC-304. One study, HSC-306, was one two-dose study and two studies, HSC-151 and HSC-305 were one-week studies. There were four placebo-controlled studies, HSC-303, HSC-304, HSC-305, and HSC-306. The duration of treatment exposure is also displayed in Table 9.2.1.

In this reviewer's opinion, treatment exposure in the clinical development program for CTC is adequate to assess safety.

Table 10.3.1 Treatment exposure in the clinical trials for development of CTC, reproduced from sponsor's Table 5-1, Volume 1.34, page 36.

Treatment	HSC-302	HSC-151	HSC-153Z	HSC-153B	HSC-303	HSC-304	HSC-305	HSC-306
Clemastine Tablet								
1 x 0.5 mg single dose	22		30			61*		
2 x 0.5 mg single dose				32				
1 x 1.0 mg single dose	11							
1 x 0.5 mg q6h, 1 week		22						
1 x 0.5 mg q6h, 1 week							136	
1 x 1.0 mg q12h, 1 week							135	
Tavist-1®								
1 x 1.0 mg single dose	11			32				
1 x 1.0 mg BID, 1 week		22						
Tavist® (clemastine) Syrup								
1 x 0.25 mg single dose					24			
1 x 0.5 mg single dose			29		24			
1 x 1.0 mg single dose					24			

Treatment	HSC-302	HSC-151	HSC-152	HSC-153B	HSC-303	HSC-304	HSC-305	HSC-306
Clemastine Triple Combination (CTC)								
2 tablets			30					118**
4 tablets				32				
TheraFlu® Sinus								
2 tablets, 2 doses			30					119
Combination Treatment								
2 x 0.5 mg clemastine plus 4 x TheraFlu® Sinus				31				
Placebo					24	20	138	61
Total Number of Subjects Enrolled	22	22	32	32	24	21	412	298
Never received drug	0	0	0	0	0	0	3	0
Discontinued early	0	0	2	1	0	1	37	4

*single dose of 0.5mg clemastine given in each of three periods at 1 hr (20 subjects), 4 hr (21 subjects), or 6 hr (20 subjects) before intranasal challenge
**Two doses of CTC given

The mean age of patients for all studies was 29 years, with a range of 12-67 years. The majority of these patients were male and Caucasian (Table 10.3.2).

Table 10.3.2 Demographics for clinical trials for development of CTC, compiled from sponsor's Tables 6-1 and 6-2, Volume 1.34, pages 37 and 38.

Characteristic	HSC-302 (N=22)	HSC-151 (N=22)	HSC-152 (N=32)	HSC-153B (N=32)	HSC-303 (N=24)	HSC-304 (N=21)	HSC-305 (N=412)	HSC-306 (N=298)	Total* (N=863)
Age (years)									
Mean	27	28	30	33	29	26	33	28	29
Range	19-41	19-49	19-50	19-49	19-45	18-36	12-67	12-62	12-67
Gender, % Male	100	100	50	100	100	76	42	45	78
Race, % Caucasian	95	91	91	88	96	71	85	81	87

*Mean, Gender, and Race in Totals column derived from weighted averages from sponsor's Table 6-1 and 6-2.

10.3.2. AEs

AEs in PK and PD studies were integrated and analyzed separately from AEs in pivotal controlled clinical trials HSC-305 and HSC-306. AEs occurring most frequently and in more than 10% of patients in PK and PD studies were rhinitis, headache, nausea, pharyngitis and sore throat, and fatigue. Nausea, fatigue, asthenia, dizziness, drowsiness, abdominal pain, dry mouth, and nervousness were AEs noted in PK and PD studies that were also noted in the controlled clinical trials HSC-305 and HSC-306. These data are displayed in Table 10.3.3.

Table 10.3.3 Adverse events occurring in clemastine-treated patients in PK and PD studies.

Adverse event	N=153 n	(%)
Rhinitis, URI	33	(21.6)
Headache	25	(16.3)
[redacted]	[redacted]	[redacted]
Pharyngitis, sore throat	21	(13.7)
[redacted]	[redacted]	[redacted]
Hot flushes	7	(4.6)
Pain	7	(4.6)
[redacted]	[redacted]	[redacted]
Diarrhea	5	(3.3)
Coughing	5	(3.3)
Nose dry	4	(2.6)
Accidental injury	3	(2.0)
[redacted]	[redacted]	[redacted]

*Bold and highlighted AEs are noted in one or both of the clinical studies HSC-305 and 306, Tables 10.3.4. and 10.3.5.

AEs were examined separately for controlled clinical trials HSC-305 and HSC-306 because of large differences in the study designs. HSC-305 was a one-week multidose study with clemastine 0.5 mg tablets, and HSC-306 was a one-day, two-dose study with the CTC formulation. AEs in HSC-305 occurring in ≥ 2% of patients taking clemastine and more frequently than placebo are listed in Table 10.3.4. Headache, somnolence, fatigue occurred in more than 10% of patients taking clemastine. There was a dose-response effect noted for somnolence, fatigue, dry mouth, and dizziness.

Table 10.3.4 HSC-305, adverse events occurring in ≥2% of patients taking clemastine and more frequently than placebo [Volume 1.26, pages 38, 39]

Adverse Event	Clemastine 0.5 mg QID, N=136 n	(%)	Clemastine 1.0 mg BID, N=135 n	(%)	Placebo, N=138 n	(%)
Headache	66	(48.5)	67	(49.6)	63	(45.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	5	(3.7)	3	(2.2)	1	(0.7)
Influenza-like symptoms	6	(4.4)	2	(1.5)	0	(0)
Abdominal pain	4	(2.9)	2	(1.5)	0	(0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth disorder	3	(2.2)	2	(1.5)	0	(0)
Vomiting	4	(2.9)	0	(0)	0	(0)
Arthralgia	0	(0)	3	(2.2)	0	(0)
All events	96	(70.6)	100	(74.1)	91	(65.9)

*Bold and highlighted AEs had a dose-response effect noted.

AEs in HSC-306 occurring more than once in patients taking CTC and more frequently than placebo are listed in Table 10.3.5. Somnolence, fatigue, and nervousness were the most common AEs occurring in this study. It should be noted that somnolence or drowsiness and fatigue were also noted in HSC-305 and in the PK and PD studies.

Table 10.3.5 HSC-306, adverse events occurring in more than one patient taking clemastine and more frequently than placebo [Volume 1.29, page 20]

Adverse Event	CTC N=118		TF Sinus N=119		Placebo N=61	
	n	(%)	n	(%)	n	(%)
Somnolence	22	(18.6)	7	(5.9)	0	(0)
Fatigue	6	(5.1)	7	(5.9)	1	(1.6)
Nervousness	2	(1.7)	0	(0)	0	(0)
All events	40	(33.9)	31	(26.1)	11	(18.1)

AEs considered by the sponsor to be treatment-related were similar to those displayed in Tables 10.3.3., 10.3.4., and 10.3.5. These AEs included somnolence, fatigue, dyspepsia, headache, and dry mouth [Volume 1.34, pages 93-111].

Drowsiness or somnolence, fatigue, dry mouth, dyspepsia, abdominal pain, and nausea are AEs that are known to be associated with first generation antihistamines and would be expected to be seen with clemastine. Dry mouth is an manifestation of the anticholinergic properties of clemastine. These AEs do not reveal any new safety signal for clemastine.

10.3.3. SAEs and deaths

There were no SAEs or deaths in any of the studies included with this application.

10.3.4. Withdrawals

There were two withdrawals due to AEs in clemastine-treated patients in the PK studies. One had itching, rash, nausea, and pallor and another had vomiting.

Somnolence and fatigue were common reasons for withdrawal for clemastine-treated patients in HSC-305, a one-week multidose study. There was a dose response effect seen in the number of patients withdrawing from the study for these AEs. There were no withdrawals in studies HSC-303, HSC-304, and HSC-306. Somnolence, fatigue, nausea, rash, and vomiting have been reported with clemastine and other first generation antihistamines. These data do not reveal any new safety signal for clemastine.

10.3.5. Vital signs and physical examination

Small and clinically insignificant increases in pulse were seen in studies HSC-303 and HSC-305. These are likely to be related to the anticholinergic effects of clemastine and are not likely to represent a safety concern. Elevated BP was seen in the PK studies and in HSC-303. Two patients had significantly elevated BPs in the PK studies, one who had a BP 189/127. Both of these patients were taking clemastine alone, and were not taking pseudoephedrine. Elevated BP may represent a new safety signal for clemastine.

10.3.6. Laboratory studies

The only laboratory abnormality seen with any consistency in the studies included in this application was elevated CPK, and this was rare. Four clemastine-treated patients developed elevated CPKs. These were patients 0632 and 0615 in placebo-controlled study HSC-305, patient 16 in HSC-302, and patient 008 in HSC-151. There was little difference in the percent of patients with a change in CPK from normal to abnormal between clemastine and placebo in the only placebo-controlled study in this application that had laboratory studies performed

as safety endpoints, HSC-305. The change in CPK from normal to abnormal was 6.7% (18/270) in clemastine-treated patients and 5.9% (8/136) in placebo-treated patients in this study. These data are listed in Tables 10.3.6. and 10.3.7.

Table 10.3.6 List of patients with change in CPK from normal to abnormal, parallel group, placebo-controlled study HSC-305.

Patient Number	Treatment	Baseline Visit 0 CPK, U/L	Final Visit CPK, U/L	Follow-up CPK, U/L
HSC-305	Parallel group Placebo controlled 3 arms			
0821	0.5 mg clemastine QID	151	183	ND*
1134	0.5 mg clemastine QID	138	203	ND
1002	0.5 mg clemastine QID	139	205	ND
0903	0.5 mg clemastine QID	193	238	ND
0904	0.5 mg clemastine QID	143	225	ND
0608	0.5 mg clemastine QID	121	183	ND
0618	0.5 mg clemastine QID	87	215	ND
0620	0.5 mg clemastine QID	148	421	ND
0632	**0.5 mg clemastine QID**	**125**	**1049**	**ND**
0502	0.5 mg clemastine QID	75	205	ND
0515	0.5 mg clemastine QID	175	218	ND
0830	1.0 mg clemastine BID	135	346	ND
0835	1.0 mg clemastine BID	72	191	ND
1112	1.0 mg clemastine BID	159	217	ND
1012	1.0 mg clemastine BID	129	231	ND
0936	1.0 mg clemastine BID	139	214	ND
0615	**1.0 mg clemastine BID**	**158**	**1259**	**ND**
0426	1.0 mg clemastine BID	187	294	ND
0117	Placebo	155	189	ND
1015	Placebo	156	241	ND
0509	Placebo	166	226	ND
0518	Placebo	108	245	ND
0208	Placebo	167	231	ND
0212	Placebo	115	178	ND
0220	Placebo	113	289	ND
0703	Placebo	166	863	ND

*ND = not done
**Bold and highlighted entries have CPK levels >1000.

Table 10.3.7 List of patients with change in CPK from normal to abnormal, crossover studies. All patients treated with clemastine, labs performed at baseline and at end of study.

Study and Design	Patient Number	Baseline Visit 0 CPK, U/L	Final Visit CPK, U/L	Follow-up CPK, U/L
HSC-306				
	No labs performed			
HSC-303 4 period crossover Placebo, 0.25 mg clemastine, 0.5 mg clemastine, 1.0 mg clemastine				
	12	[		]
	20			
HSC-304 4 period crossover 0.5 mg clemastine given at different times				
	014	[		]
	019			

Study and Design	Patient Number	Baseline Visit 0 CPK-U/L	Final Visit 4 CPK-U/L	Follow-Up CPK-U/L
HSC-302 2 period crossover 0.5 mg clemastine 1.0 mg clemastine	[redacted]	[redacted]		
HSC-151 2 period crossover 0.5 mg clemastine 1.0 mg clemastine	006 [redacted] 020	[redacted]		
HSC-152	None with change from normal->abnormal			
HSC-153B 4 way crossover CTC, 1.0 mg clemastine, 1.0 mg clemastine plus TF Sinus, 2 x 0.5 mg clemastine	15 21 26	[redacted]		

*Bold and highlighted entries have CPK levels >1000.
**ND = Not done

Shift table analysis was performed for CPKs in patients in all studies. The percentage of patients with a shift upwards in CPK in clemastine- and placebo-treated groups were similar. There were 7.1% (29/408) of clemastine-treated patients with a shift upwards in CPK compared with 8.1% (11/136) of placebo-treated patients. These data are displayed in Table 10.3.8.

Table 10.3.8 Shift table, patients with change in CPK from baseline to final visit, all studies integrated.

Treatment	Baseline	Final		
		Low	Normal	High
Clemastine*	Low	6	[redacted]	[redacted]
	Normal	0	333	[redacted]
	High	0	18	22
Placebo	Low	1	[redacted]	[redacted]
	Normal	3	99	[redacted]
	High	0	12	10

*Includes all clemastine-treated patients, regardless of dosage form.

The cause of the elevated CPK levels in there patients is unclear. It is reassuring that the rate of change in CPK from normal to abnormal in the placebo-controlled study and the shift table analysis showed little difference between clemastine-treated patients and placebo-treated patients.

10.3.7. ECGs

There were no clinically significant changes in ECGs in any of the studies included in this submission.

10.4. Spontaneous AE reports

AEs, SAEs, deaths, and overdose reports identified in a search of the Agency's Spontaneous Reporting System (SRS) database are reviewed in the following sections of this review.

10.4.1. AEs

The sponsor presented AEs identified in a search of the Agency's Spontaneous Reporting System (SRS) database. The sponsor presented AEs where Tavist or clemastine was a suspect drug. The period searched was 1969 until October 1997 when the database was closed and the AERS database was started. A total of 1067 cases with 1926 individual AEs were identified. The most commonly reported AEs are found in Table 10.4.1.

Table 10.4.1 Adverse events identified by the FDA SRS, 1969-1997. Adverse events ≥2.0% of all clemastine adverse events are listed [Volume 1.34, page 50].

Adverse event, COSTART term	n	% of all adverse events
Somnolence	249	12.9
Lack of drug effect	137	7.1
Dizziness	71	3.7
Headache	64	3.3
Nausea	49	2.5
Asthenia	44	2.3
Nervousness	41	2.1
Insomnia	40	2.1
Malaise	39	2.0
All AEs	1926	100

Somnolence, dizziness, headache, nausea, asthenia, nervousness, insomnia, and malaise were noted in the clinical trials, and are associated with conventional sedating antihistamines such as clemastine. These data do not identify any new safety signal.

10.4.2. SAEs

The most notable SAE identified in the SRS database was hypertension. There were 14 reports of hypertension, all of which were reported with Tavist-D, which contains ———————. It should be noted that hypertension was noted as an AE in the clinical studies in this application.

Other SAEs were presented by the sponsor, but these had various causes and there was no case clustering noted. Therefore, they are not likely to represent a new safety signal [Volume 1.34, pages 51-52].

10.4.3. Deaths

There were 13 deaths among the cases identified by the SRS from 1969 until October 1999. These deaths had various causes, and no case clustering was noted. [Volume 1.34, pages 52-53]

10.5. Overdose

There were no overdoses in any of the clinical trials in this submission. There were 42 cases in the US identified in the sponsor's database and 6 foreign cases, 3 in Germany and 3 in Switzerland [Volume 3.1, page 5].

The sponsor's listing of AEs from the Agency's SRS identifies 14 cases of overdose over the period 1969-1997. Eleven of these cases occurred after 1992, when clemastine became available as an OTC product [Volume 1.34, pages 50-51]. Of these 14 cases of overdose, six were classified as serious events in the outcome field of the database, and one resulted in death [Volume 1.34, pages 52-53].

Clemastine has been available since 1992 as an OTC product. Relatively few cases of overdose are noted in the databases above. In this reviewer's opinion, the potential risk from overdose of clemastine is outweighed by the public's benefit from drug. No label warning for overdose is necessary.

10.6. Human reproduction data

Two cases of congenital anomaly were identified sponsor's search of the SRS database, one in 1995 and one in 1997 [Volume 1.34, page 51]. Details on these cases were not provided.

This reviewer searched the AERS database for cases of congenital anomaly associated with clemastine use. Six cases were identified in this search. All had insufficient information to assess the likelihood of causality by clemastine. These cases are presented in Table 10.6.1.

Table 10.6.1 Congenital anomalies and clemastine, search of AERS database.

AERS Case number	Anomaly	Date	Concomitant medication	Manufacturer's number
1374795	Congenital anomaly NOS	September 1993	None	– 9301216TAV
1530700	Congenital anomaly NOS	December 1994	None	N9400029TAV
1556821	Congenital anomaly NOS	March 1995	None	B0009303
619593	Congenital anomaly NOS	November 1989	Distalgesic and prolutin	TAV892150USA
619595	Congenital anomaly NOS	September 1993	Oleandomycin, naladixic acid, tetracycline	TAV891251USA
3250126	Hypospadias	February 1997	Loratadine, cromolyn sodium eye drops, nasal spray	1998-07-0248

It should be noted that clemastine has been approved in Europe since 1966, in the US as a prescription product since 1977, and as an OTC product since 1992. It is unlikely that these few reports represent a true safety signal in light of the long marketing history for clemastine.

10.7. Literature survey

The sponsor performed a literature survey for the period 1995, just prior to the approval of Tavist-1 for the OTC treatment of common cold symptoms, until September 10, 1999. The sponsor searched MEDLINE with the search strategy "(Clemastine OR Tavist) AND human" for the period 1966 until present. This search identified 221 articles. The sponsor screened the abstracts of the articles from 1995 until the time of the search. There were four articles with primary safety data. They included one case report of toxic pustuloderma associated with clemastine and three articles with clinical trial results that included safety data. Dry mouth, nose, and throat were seen in one study. These are known to be anticholinergic AEs associated with clemastine. The other two clinical trials provided little safety information. This reviewer concurs with the sponsor that the literature survey provides no additional safety information and identifies no new safety concerns.

11. SPECIAL POPULATIONS

Evaluations of efficacy and safety by gender and race are described below. Children less than the age of 12 years were enrolled in studies in this application. Very small numbers of patients were over the age of 65 years, and an analysis of efficacy and safety in the elderly was not possible.

11.1. Efficacy

Women taking both doses of active drug and placebo in pivotal study HSC-305 showed greater improvement than males in the primary efficacy variables, physician and patient-assessed nasal discharge/runny nose and sneezing scores [Volume 3.2, pages 80-111]. The significance of this finding is unclear. A difference in efficacy was not noted in the other pivotal study, HSC-306 [Volume 1.29, pages 91-119]. The difference in efficacy by gender in HSC-305 may be due to chance.

No consistent difference in efficacy was seen in HSC-305 between Caucasian and non-Caucasian patients [Volume 1.34, pages 154-185]. The subgroup analysis of efficacy by race in HSC-306 showed Caucasians to have slightly smaller reductions in the MSC over hours 2-5 for CTC, TF Sinus, and placebo [Volume 3.1, page 13]. The concordant findings in the active and placebo arms in HSC-306, and the lack of similar findings in HSC-305 indicate that the decreased efficacy noted in Caucasians in study HSC-306 may be due to chance.

11.2. Safety

A higher frequency of AEs was seen in women in pivotal studies HSC-305 and HSC-306 in both the active treatment, control, and placebo groups. No particular AE was substantially more frequent in women than in men [Volume 1.34, page 112-114]. An analysis of AEs by race revealed no consistent difference between Caucasian and non-Caucasian patients that could not be explained by the small numbers [Volume 1.34, pages 125-141].

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 [Volume 1.34, pages 37-38]. Small numbers of patients in these age groups preclude a subgroup analysis of efficacy by age.

12. DSI AUDIT AND FINANCIAL DISCLOSURE

Two sites from the efficacy studies were reviewed by DSI. The sites were chosen based on the importance of the sites to this NDA. The sites were: (1) James C. Kisicki, M.D., Lincoln NE for PK studies HSC-151, HSC-152, HSC-153B, and PD study HSC-303, and (2) Thomas B. Casale, M.D., Papillion, NE, for HSC-306. Representative data from the NDA were provided to the DSI team for comparison with the original data source. Data were verified at both sites and no discrepancies were observed. The DSI inspectors concluded that the data for these studies appear acceptable for use in support of drug claims [Correspondence from DSI, March 24, 2000, April 19, 2000] .

All studies in support of this NDA were completed prior to February 2, 1999. The sponsor was required to report any outcome payments and proprietary interests of investigators. [Volume 1.1, Financial Disclosure, no page number, personal communication with David Hilfiker, DPADP Project Manager].

13. LABELING AND TRADE NAME REVIEW

Preliminary comments on proposed product labeling follow. Final product labeling will reflect final review and comments.

The proposed product labeling included in this application consisted of draft labeling for the 24 and 48 count retail package sizes. There was no proposed package insert included [Volume 1.1, pages 9-17, Volume 3.2, page 229]. This reviewer compared labeling for the new combination drug product with current labeling for Tavist Allergy 12 Hour Tablets® (clemastine 0.5 mg) and Tavist® Sinus Caplets (acetaminophen 500 mg and pseudoephedrine 30 mg), as posted in the PDR Electronic Library, Medical Economics Company, Inc., 2000, www.pdrel.com .

——— should be deleted from the Uses section because there were no clinical data submitted to support use for this indication.

Drowsiness is listed in the Warnings section of the Drug Facts section, but in a typeface that is not bold. The drowsiness warning also is located at the right side of the Drug Facts box. Drowsiness and sedation are very common AEs noted with clemastine, and this warning should be listed more prominently.

——————' is displayed inside a seal on the front of the package. This seal should be deleted, as it implies that other similar products may not be as reliable.

The front of the package displays the statement ——— This is an unsubstantiated onset of action claim which should be deleted.

Proposed product labeling appears otherwise acceptable.

The Office of Post-Marketing Drug Risk Assessment (OPDRA) was consulted to conduct a review of the proposed proprietary name "Tavist/Allergy/Sinus/Headache" to determine the potential for confusion with approved proprietary and generic as well as pending names

[Consultation response, Jerry Phillips, R.Ph., 4/27/00]. OPDRA did not object to the use of the proposed name, but did have a concerns that several "Tavist" brand products are marketed in the US and that there is the potential for consumer confusion among the different products. OPDRA also noted that the sponsor encoded the proposed indications into the trade name. However, the Agency has no regulatory authority for OTC drug product advertising and promotion and OPDRA recommended no trade name change. OPDRA did recommend that a footnote should be added to the front panel in which the sponsor defines caplet as being a "capsule-shaped tablet" because it is not an official USP dosage form.

Hilfiker

JAN - 3 2000

Application Number: 21-082		**Application Type:** NDA	
Sponsor: Novartis Consumer Health, Inc.		**Proprietary Name:** Tavist® Allergy/Sinus/Headache	
Category of Drug:	antihistamine/ decongestant/ analgesic/ antipyretic	**USAN Name:**	Clemastine fumarate/ acetaminophen/ pseudoephedrine HCl
		Route of Administration: Oral	
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	12/14/99

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	10/7/99	**Submission Type:**	NDA
CDER Stamp Date:	10/8/99	**Comments:**	

RELATED APPLICATIONS (if applicable):

Document:	Date:
NDA 17-661	2/25/77
NDA 18-675	6/28/85
NDA 18-298	8/21/92

REVIEW SUMMARY:

This is a 45 day clinical filing review of NDA 21-082, clemastine fumarate 0.25 mg/acetaminophen 500 mg/pseudoephedrine HCl 30 mg caplets (Tavist® Allergy/Sinus/Headache). The proposed indications include temporary relief of symptoms associated with allergic rhinitis, the common cold, ——— The submission contains 4 PK studies, 2 skin test suppression pharmacodynamics studies, and 2 pivotal clinical efficacy and safety studies. The submission is adequate to allow full, in-depth clinical review. The submission is fileable.

APPEARS THIS WAY
ON ORIGINAL

OUTSTANDING ISSUES:

Awaiting details describing data entry discrepancies in study HSC-305. DSI audit may be necessary for selected sites in this study.

RECOMMENDED REGULATORY ACTION:

N drive location:

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

SIGNED:

Medical Reviewer: /S/ **Date:** 12/29/99

Medical Team Leader: /S/ **Date:** 1/3/00

I. General Information and Background

This NDA submission is for a fixed drug combination product containing clemastine base 0.25 mg (equivalent to 0.335 mg clemastine fumarate), acetaminophen 500 mg, and pseudoephedrine HCl 30 mg in a caplet form (Clemastine Triple Combination, CTC, or proposed trade name TAVIST® ALLERGY/SINUS/HEADACHE). The sponsor is Novartis Consumer Health, Inc.

The proposed dose for adults and children 12 years of age and older is 2 caplets every 6 hours as needed, and not more than 8 caplets in 24 hours unless directed by a doctor. It is not proposed for use in children under 12 years of age.

The proposed indications are:

- Temporary relief of sneezing, runny nose, and itching of the nose or throat and itchy watery eyes due to hay fever (allergic rhinitis), and sneezing and runny nose due to the common cold
- Temporary relief of nasal and sinus congestion due to the common cold, hay fever, or other upper respiratory allergies or ———
- Temporary relief of minor aches, pains, headache, ———, and fever associated with the common cold; temporary relief of minor aches, pains and headache associated with hay fever, allergic rhinitis, and ———

The tentative final monograph for combination cough, cold, and allergy drug products ("Monograph," 53 FR 30522) details combinations of active ingredients permitted for OTC cough, cold, and allergy drug products. Monograph requirements are met for this product by use of pseudoephedrine (PSE) 60 mg immediate release PO Q4-6H in adults and children ages 12 and older. Monograph requirements are met for this product by use of acetaminophen (APAP) 1000 mg immediate release Q6H in adults and children ages 12 years and older. Clemastine is not an antihistamine listed in the Monograph, and clemastine has not been approved for use at a frequency less than Q12H in any other product. A new NDA is therefore required.

Critical issues to establish for this fixed drug combination included:

- Demonstration of absence of interaction among each of the components
- Demonstration that clemastine is effective at the dose and frequency of 0.5 mg PO Q6H
- Demonstration that clemastine at the dose and frequency of 0.5 mg PO Q6H has a safety profile comparable to that of clemastine at the approved dose of 1 mg PO Q12H.

II. History and Foreign Marketing History

Clemastine was approved for use in the US on 2/25/77 as Tavist®, clemastine base 2 mg (NDA# 17-661). Tavist® syrup, clemastine base 0.5 mg/5 ml, was approved in the US on 6/28/85 (NDA# 18-675). Tavist-1®, clemastine base 1 mg, was approved in the US as an OTC product for symptoms of allergic rhinitis on 8/21/92 (NDA# 18-298). In 1996, Tavist-1® was approved for temporary relief of runny nose and sneezing associated with

the common cold. Clemastine has also been approved for OTC use as a combination product containing 1 mg clemastine plus 75 mg extended-release phenylpropanolamine (Tavist-D®).

Clemastine was first marketed in Europe as a prescription drug in 1966. Clemastine has been approved as AllerEze Plus® (0.5 mg clemastine base and 25 mg phenylpropanolamine) in the UK in 1986 and in Ireland in 1987. Clemastine has been approved in at least one oral dose form in 127 countries worldwide.

III. Items required for filing and reviewer comments (21 CFR 314.50)

The following items are included in this submission:

- Form FDA 356h
- Debarment certification
- List of referenced INDs, NDAs, and DMFs
- Financial disclosure statement
- Statement of Good Clinical Practice
- Proposed labeling
- Integrated Summary of Efficacy (ISE)
- Integrated Summary of Safety (ISS)
  - This submission includes an ISS, but the ISS does not contain any spontaneous AE reports after 10/1997. Subset analysis is performed by gender only in Studies HSC-305 and 306. A large majority of subjects in studies were male (132 of 153). All studies include only limited subgroup analyses by race.
- Integrated Summary of Benefits and Risks (ISBR)
- Literature review
- Proposed labeling
- Pediatric study requirement
  - The sponsor requests a waiver of the pediatric study requirement. The sponsor states that the product would not result in a significant improvement for use in pediatric population compared to currently marketed products. The sponsor also states that the drug clemastine fumarate has never been studied in children under 12 years of age, and that the drug has not been labeled for use in the pediatric population under 12 years of age (Volume 1, Certification statement, page not numbered). Contrary to this statement, clemastine has been studied in children and was approved for use in children ages 6 years to 12 years in NDA# 18-675, clemastine syrup 5 mg/ml.

The following item is not included in this submission:

- Environmental assessment

IV. Clinical Studies

There are 8 clinical studies included in this application. The studies include 4 pharmacokinetics (PK) and bioavailability studies, 2 pharmacodynamics (PD) skin test suppression studies, and 2 controlled clinical efficacy and safety studies. These studies are summarized in Table 1. More detailed descriptions of these studies follow below.

A. Clinical pharmacology PK and bioavailability studies

All of the PK and bioavailability studies are appropriately indexed and organized to allow review. These studies will receive brief review from the clinical reviewer and will receive in-depth review by the biopharmacology reviewer.

1. HSC-302 (Volumes 9, 10)

The objective of HSC-302 was to determine the bioavailability and dose proportionality of single doses of 0.5 mg clemastine and 1.0 mg clemastine in healthy males. It was 2 period crossover, single dose study performed on 2 separate days. There was a 7 day washout. Subjects were 22 healthy males. Safety endpoints included AEs, CBC, hematology, chemistry, UA, PE, VS.

2. HSC-151 (Volumes 11, 12)

The objective of HSC-151 was to assess the steady state pharmacokinetics of 0.5 mg clemastine BID vs. Tavist-1® (1.0 mg clemastine) BID and the compare the bioavailability of clemastine 0.5 mg QID with Tavist-1®, clemastine 1.0 mg, BID. It was an open label, 2-way crossover study in 22 healthy males, 7 days each period, with a total duration of 17 days. Safety endpoints include VS, ECG, hematology, chemistry, UA, and AEs.

3. HSC-152 (Volumes 13-16)

The objective of HSC-152 was to assess possible interactions between clemastine, PSE, APAP and to show the bioequivalence of clemastine tablets and CTC tablets. It was an open label, 4-way crossover study comparing 2 CTC tablets, one 0.5 mg clemastine tablet, 5 ml Tavist® syrup (0.5 mg clemastine), and 2 Thera-Flu® tablets (APAP 500 mg plus PSE 30 mg). Subjects were 32 healthy males and females. Safety endpoints included VS, ECG, hematology, chemistry, UA, AEs.

4. HSC-153B (Volumes 17-21)

The objective of this study was to compare single doses of 4 CTC tablets, 2 clemastine 0.5 mg tablets, 2 clemastine 0.5 mg tablets plus 4 Thera-Flu® tablets (APAP 500 mg plus PSE 30 mg per tablet) and 1 Tavist-1® tablet (1.0 mg clemastine). It was an open label, 4 way crossover study. Subjects were 32 males. Safety endpoints included VS, ECG, hematology, chemistry, UA, and AEs.

Table 1. Summary of studies, NDA 21-082

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects
HSC-302	PK, bioavailability	1 clemastine tab 0.5 mg 1 clemastine 1 mg	Single dose	2 period crossover	22
HSC-151	PK, biovavailability	1 clemastine tab 0.5 mg QID 1 clemastine tab 1 mg BID	7 days each period	2 period crossover	22
HSC-152	PK, bioavailability	2 CTC tabs 1 clemastine tab 0.5 mg clemastine syrup 0.5mg 2 Thera-Flu® tabs	Single dose 7 day washout	4 way crossover	32
HSC-153B	PK, bioavailability	4 CTC tabs 2 clemastine tabs 0.5 mg 2 clemastine tabs 0.5 mg plus 4 Thera-Flu® tabs 1 clemastine tab 1.0 mg (Tavist-1®	Single dose 7 day washout	4 way crossover	32
HSC-303	PD Skin test suppression	clemastine syrup 0.25 mg clemastine syrup 0.5 mg clemastine syrup 1.0 mg placebo	Single dose	DB, Randomized, PC, crossover	24
HSC-304	PD Skin test suppression Intranasal challenge	1 clemastine 0.5 mg tablet placebo	Single dose	DB, randomized, PC, crossover	21
HSC-305	Pivotal efficacy and safety study	1 clemastine tab 0.5 mg QID 1 clemastine tab 1.0 mg BID placebo	Multiple dose, 14 days	DB, randomized, PC, parallel group, 12 centers	412
HSC-306	Pivotal efficacy and safety study	2 CTC tabs 2 Thera-Flu® tabs placebo	One day, 2 dose	2 centers DB, randomized, PC, double-dummy, "Day in the Park" study	298

B. Clinical pharmacology PD studies

The PD studies are appropriately indexed and organized to allow review. They will receive brief reviews from the clinical reviewer because of the limited clinical relevance of the skin test suppression and nasal challenge models.

1. HSC-303 (Volume 23)

The objective of this study was to establish the minimal effective dose of clemastine. It was a double-blind, placebo-controlled, randomized, crossover, single dose, skin test suppression study. It was performed at a single center. Subjects were 24 healthy males. Clemastine syrup 0.25 mg, 0.5 mg, and 1.0 mg were studied. Safety endpoints included VS, hematology, chemistry, UA, ECG, and AEs

2. HSC-304 (Volume 24)

HSC-304 was a randomized, single-center, double-blind, placebo-controlled, crossover study. It was single dose study and treatment groups included clemastine 0.5 mg tablet and placebo . There were 21 subjects with seasonal allergic rhinitis (SAR). This study was a skin test suppression study and an intranasal challenge study. Safety endpoints included PE, VS, hematology, chemistry, UA, and AEs.

C. Controlled clinical studies

There are two pivotal controlled clinical studies included in this submission. Both are appropriately organized and indexed and both will receive in-depth review.

1. HSC-305 (Volumes 26-28)

This is a pivotal efficacy and safety study. It was a multi-center, double-blind, placebo-controlled, double-dummy, randomized, parallel group study of 14 days duration. There were 12 centers, and 412 patients ages 12-67 were enrolled. Clemastine 0.5 mg, 1 tablet QID, clemastine 1.0 mg, 1 tablet PO BID, and placebo were studied. The primary efficacy variables were patient and physician evaluation of nasal discharge/runny nose, sneezing at day 4, 8, and 15. Patients recorded instantaneous and reflective symptoms. Secondary efficacy variables included patient and physician evaluation of nasal congestion/stuffiness, nasal itching, itchy/burning eyes, tearing watering eyes, redness of eyes, and itching of ears and/or palate. Safety endpoints included VS, hematology, chemistry, UA, and AEs. ECGs were not performed. There was a problem with the data entry for this study. The sponsor found that corrections were made to the original Case Report Forms (CRFs). These corrections were not made in the electronic database from which the study report was written. This problem required re-entry and re-analysis of the data, and the report was re-written (Volume 1.26, page 4).

2. HSC-306 (Volumes 29-32)

This is a pivotal efficacy and safety study. It seeks to show the first dose efficacy and onset of action of the CTC tablet. It was a 1 day, multicenter, randomized, double-blind, double-dummy, placebo-controlled, "day in the park" study in 298 subjects with SAR. It was performed at 2 centers. Treatment groups were 2 CTC tablets, 2 Thera-Flu® tablets

(APAP 500 mg plus PSE 30 mg), and placebo were studied. Primary efficacy variables were patients' assessments of the major symptom complex (MSC). The MSC was the sum of the severity scores of the patients' assessments of sneezing, itchy nose, watery eyes, itchy eyes/ears, and itchy throat. Secondary efficacy variables included total symptom complex (the MSC score plus patients' assessments of nose blows, sniffles, post-nasal, drip and cough). Safety endpoints included AEs. There were no VS, laboratory studies, or ECGs.

V. Brief review of proposed labeling

The product name TAVIST® ALLERGY/SINUS/HEADACHE will require discussion at the labeling review meeting because of the potential for confusion with other Tavist® products.

VI. DSI Review/Audit

H. W. Ju, M.D. of DSI has been notified that the following sites have been identified for inspection:

- James Kisicki, M.D., Lincoln, NE, the site of 4 studies, HSC-151, HSC-152, HSC-153B, and HSC-303
- Thomas Casale, M.D., Papillion, NE, one of the two sites in the "day in the park" study, HSC-306

Other sites may be inspected depending on the additional information requested on the re-entry, re-analysis, and rewriting of the report of study HSC-305.

VII. Time Line for Review

Write-up will be concomitant with the review process. Review of efficacy and safety will be performed for each study before moving to the next study. The pharmacokinetics studies HSC-302, HSC-151, HSC-152, and HSC-153B will be reviewed first, allowing 2 weeks for these studies. The skin test suppression studies, HSC-303 and HSC-304 will be reviewed next, allowing two weeks for these studies. The pivotal efficacy and safety studies, HSC-305 and HSC-306 will be reviewed next in order, allowing 2 weeks for each study. Review of the integrated summaries of safety, efficacy, and benefits and risks will be completed next. Label review will be complete by 5/12/00. Draft review will be complete by 5/26/00, allowing 2 weeks for DPADP review and time for comments and suggestions before the combined DPADP and DOTC labeling meeting, which is scheduled for 6/12/00.

Table 2. Proposed Schedule for Review of NDA 21-082

Study HSC-305	2/11/00
Study HSC-306	2/25/00
Studies HSC-302, HSC-151, HSC-152, HSC-153B	3/10/00
Studies HSC-303, HSC-304	3/24/00
Integrated Summaries of Efficacy	4/7/00

Integrated Summary of Safety	4/14/00
Integrated Summary of Risk and Benefits	4/28/00
Label Review	5/12/00
Draft review	5/26/00

Reviewed by:

/S/

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

/S/ 1/3/00

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

cc: Original NDA
HFD-570/Division File
HFD-570/Meyer/Division Director
HFD-570/ Chowdhury/Acting Team Leader
HFD-570/Lee/Medical Reviewer
HFD-715/Elsahoff/Statistics Reviewer
HFD-570/Khorshidi/Chemistry Reviewer
HFD-570/Chun/Pharmacology-Toxicology Reviewer
HFD-570/Chen/Biopharmacology Reviewer
HFD-560/Hu/OTC/Medical Reviewer
HFD-560/Merritt/OTC/CSO
HFD-570/Hilfiker/CSO

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

Application Number:	21-082	**Application Type:**	NDA
Sponsor:	Novartis Consumer Health, Inc.	**Proprietary Name:**	Tavist®Allergy/Sinus/Headache
Category of Drug:	Antihistamine/ decongestant/ analgesic/ antipyretic	**USAN Name:**	Clemastine fumarate/ acetaminophen/ pseudoephedrine HCl
		Route of Administration:	Oral
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	2/26/01

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type, Comments:
NDA 21-082	10/7/00	10/8/00	Request for waiver of pediatric studies, original submission

RELATED APPLICATIONS (if applicable):

Document Date:	Application Type:	Application Number:	Comments:
2/25/77	NDA	17-661	Tavist® 2.68 mg tablets
6/28/85	NDA	18-675	Tavist syrup
8/21/92	NDA	20-925	Tavist-1, OTC, 1.34 mg tablets
8/21/92	NDA	18-298	Tavist-D, OTC
8/9/96	NDA	20-640	Tavist-D, [redacted], OTC

REVIEW SUMMARY:

NDA 21-082, Tavist® Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/30 mg pseudoephedrine HCl) was submitted 10/7/99 by Novartis Consumer Health, Inc. The original NDA submission provided adequate evidence of safety and efficacy for the temporary relief of various nasal and ocular symptoms associated with the hay fever, allergic rhinitis, and the common cold. The Division of Pulmonary and Allergy Drug Products took an approvable action on 8/4/00, and the Division is considering a second cycle approvable action. The sponsor's request for waiver of pediatric studies is an outstanding issue for this application. The sponsor believes this product would not be a significant improvement over adequately labeled, currently marketed products, and has requested a waiver of the pediatric study requirement. This request for waiver is reviewed below.

The 500-mg dose of acetaminophen in one tablet of this product exceeds the currently accepted acetaminophen dose of 15mg/kg, based on 50th percentile weights for patients 12 years of age. Therefore, one tablet of this product contains a dose of acetaminophen that is not appropriate for children under 12 years of age. There are no products containing acetaminophen at 500 mg/tablet approved for use in children under 12 years of age. This reviewer believes that it is not medically appropriate to obtain pediatric data on this combination product. In addition, this reviewer concurs with the sponsor's opinion that the product would not be a significant improvement over currently marketed products. This reviewer recommends granting a waiver of pediatric studies.

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: **Date:**

Medical Team Leader: **Date:**

/s/

Charles Lee
2/26/01 01:46:28 PM
MEDICAL OFFICER

Mary Purucker
2/26/01 07:18:52 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL