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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-297

Statistical Review(s)

Statistical Review and Evaluation
Clinical Studies

NDA #: 21-297
Applicant: Schering Corporation
Name of Drug: Clarinex (Desloratadine) 5 mg Tablets
Indication: Chronic Idiopathic Urticaria in Adults and Adolescents
Documents Reviewed: Volumes 1.1, 1.18-1.27 and data dated August 30, 2000

This review pertains to the evaluation of two Phase 3 studies in patients with chronic idiopathic urticaria (CIU).

The medical officer for this submission is C. Rosebraugh, M.D. (HFD-570), with whom this review was discussed.

I. Background

Desloratadine is the major active metabolite of loratadine, marketed in the U.S. as Claritin. Desloratadine will be denoted as DL throughout this review. Desloratadine is currently under review for the SAR indication. Since it was not approved at the time of this submission, it was submitted as a new NDA, rather than as a supplement.

Since these two studies used identical protocols, they will be jointly discussed.

II. Chronic Idiopathic Urticaria Studies

A. Study Description and Method of Analyses

These studies were randomized, placebo-controlled, parallel group studies in adults and adolescents with chronic idiopathic urticaria with a 6-week treatment period. They compared DL 5.0 mg given QD in the morning with placebo.

At baseline and during treatment, subjects assessed the severity of the signs and symptoms of CIU (pruritus, number of hives, and size of largest hive) twice daily in a diary, describing status over the previous 12 hours (PRIOR) and status at the time of assessment (NOW). In addition, subjects assessed interference with sleep and daily activities. Pruritus, interference with sleep, and interference with daily activities were scored according to a 4-point scale (0=none, 1=mild, 2=moderate, and 3=severe). The number of hives were scored as follows: 0=none, 1=1 to 6 hives, 2=7 to 12 hives, 3= >12 hives. The size of the largest hive was scored as follows: 0=none, 1=less than 1.25 cm (<0.5 inch) diameter, 2=1.25 to 2.5 cm (0.5-1.0 inches) diameter, 3=greater than 2.5 cm (>1 inch) diameter.

Keywords: Clinical Studies, NDA review

The subject and the investigator reviewed the diary and jointly assessed the overall condition of CIU at baseline and at all subsequent visits, according to the 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). The score was based on the entire interval since the previous visit, up to, and including, the current time.

Therapeutic response to treatment was based on review of symptom scores for the entire time interval since the previous visit, up to, and including, the current time. The subject and investigator jointly graded the signs and symptoms according to the following criteria: 1=complete relief; 2=marked relief; 3=moderate relief; 4=slight relief; or 5=treatment failure.

The primary efficacy variable was the average AM/PM reflective (PRIOR 12 Hrs.) pruritus score from the patient diaries, expressed as the change from baseline value; the primary time point was the average over the first week of treatment (Days 1-8). It was analyzed using a two-way ANOVA with factors: treatment and center. In addition to the averages over each of the 6 weeks of treatment, all symptoms were analyzed for each of the first four days of treatment.

A total symptom score was created as the sum of 3 individual symptoms scores (pruritus, number of hive, and size of largest hive).

The subjects were required to have experienced a current flare of their CIU for ≥3 weeks prior to their screening visit. Hives had to be present on at least 3 days per week, during this current flare prior to the screening visit.

To enter the study, subjects had to have at least moderate pruritus (score of ≥2), and their hives were to have been present (score of ≥1) at screening and at baseline, and have had a total score of ≥14 [sum of AM and PM reflective scores (PRIOR 12 Hrs.) for the 3 days prior to baseline and the AM reflective score on Day 1]. The subjects overall condition was to have been at least moderate (score of ≥2) at screening and baseline visit.

Each of the studies was designed to enroll a total of 200 subjects (100 per treatment group). The sample size was chosen to detect (with 90% power and 5% significance level) a difference of 0.5 units in the mean change from baseline in pruritus (PRIOR 12 Hrs.), assuming a pooled standard deviation of 1.0.

B. Results

1. Study P00220

There were 226 subjects (116 DL 5.0 mg and 110 placebo) randomized at 25 centers. A total of 54 subjects (19 DL 5.0 mg and 35 placebo) failed to complete the study, mostly for treatment failure (14 DL 5.0 mg and 29 placebo). The primary efficacy analysis used data from 225 subjects.

The treatment groups were comparable at baseline in demographic variables and baseline efficacy variables. The patients were mostly females (75%) and Caucasians (70%).

One DL 5.0 mg patient had no post-baseline diary data. The sponsor excluded this patient for all diary variables.

The test of treatment-by-center interaction was not significant (p=0.25) for the primary efficacy analysis. Study centers 02, 05, 25, and 31 were pooled together for this analysis only because of the small number of subjects at these centers.

Table 1 contains the results of the analysis of the primary efficacy variable pruritus (PRIOR 12 hours) (AM/PM average). Significant differences favoring DL 5.0 mg were seen at Days 1-8, Days 2 through 4, Days 9-15, Days 16-22, and Days 23-29.

Similar significance was seen in the analyses of number of hives and size of largest hive (AM/PM PRIOR 12 Hrs) (Tables 2 and 3).

Table 4 contains the results of the analysis of pruritus (AM NOW). Significant differences favoring DL over placebo were seen on Days 2-8, Days 2 through 4, and Days 9-15.

2. Study P00221

There were 190 subjects (95 DL 5.0 mg and 95 placebo) randomized at 27 centers. A total of 51 subjects (19 DL 5.0 mg and 32 placebo) failed to complete the study, mostly for treatment failure (13 DL 5.0 mg and 21 placebo). The primary efficacy analysis used data from 189 subjects.

The treatment groups were comparable at baseline in demographic variables and baseline efficacy variables. The patients were mostly females (75%) and Caucasians (87%).

One placebo patient lost diary data for the first 2 weeks. The sponsor excluded this patient for all diary variables. (This patient had no data for the primary efficacy analysis.)

The test of treatment-by-center interaction was not significant (p=0.29) for the primary efficacy analysis. Study centers 14, 19, 22, 23, 25, and 27 were pooled together for this analysis because of the small number of subjects at these centers.

Table 5 contains the results of the analysis of the primary efficacy variable pruritus (PRIOR 12 hours) (AM/PM average). Significant differences favoring DL 5.0 mg were seen at Days 1-8 average, Days 2 through 4, and all weekly averages.

Similar significance was seen in the analyses of number of hives and size of largest hive (AM/PM PRIOR 12 Hrs) (Tables 6 and 7).

Table 8 contains the results of the analysis of pruritus (AM NOW). Significant

differences, favoring DL over placebo, were seen on Days 2-8 average, Days 2 through 4, and all weekly averages.

C. Reviewer's Comments

This reviewer verified the analysis results using the programs and data files supplied by the sponsor. The sponsor's programs and data files provided the tables included in this review.

III. Overall Comments

The sponsor demonstrated the efficacy of DL 5.0 mg for changes from baseline in AM/PM Pruritus (PRIOR 12 hours) averaged over Days 1-8, the primary efficacy analysis in both studies. Similar significance was seen in the analyses of number of hives and size of largest hive (AM/PM PRIOR 12 Hrs). Significant differences were seen in AM (NOW) Pruritus averaged over Days 2-8 in both studies, demonstrating that QD dosing of DL 5.0 mg is effective.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician

Concur: Dr. Wilson

This review contains 4 pages of text and 8 pages of tables.
cc:
Archival NDA 21-297
HFD-570
HFD-570/Dr. Rosebraugh
HFD-570/Ms. Trout
HFD-710/Dr. Anello
HFD-715/Dr. Gebert
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HFD-715/Dr. Wilson

Table 1 - Pruritus Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00220)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	115	2.19		110	2.21		0.42	0.853	0.071
Change from Baseline									
Day 1[c]	115	-0.23	(-8.7%)	110	-0.13	(-5.5%)	0.57	0.190	0.397
Day 2	114	-0.96	(-40.3%)	110	-0.44	(-13.8%)	0.88	<.001	0.236
Day 3	112	-1.08	(-47.4%)	110	-0.46	(-16.2%)	0.99	<.001	0.775
Day 4	112	-1.08	(-48.5%)	108	-0.57	(-23.3%)	0.91	<.001	0.035
Days 1-8	115	-1.05	(-47.9%)	110	-0.52	(-21.9%)	0.78	<.001	0.322
Days 9-15	107	-1.28	(-59.1%)	90	-0.85	(-39.8%)	0.86	<.001	0.312
Days 16-22	103	-1.37	(-63.3%)	83	-1.03	(-48.1%)	0.89	0.013	0.585
Days 23-29	100	-1.44	(-67.0%)	80	-1.13	(-52.9%)	0.87	0.023	0.257
Days 30-36	99	-1.44	(-66.1%)	78	-1.27	(-59.1%)	0.90	0.224	0.646
Days 37-42	96	-1.54	(-69.2%)	73	-1.28	(-58.6%)	0.90	0.076	0.701
Day 1-8	**115**	**-1.05**	**(-47.9%)**	**110**	**-0.52**	**(-21.9%)**	**0.78**	**<.001**	**0.322**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 2 - Number of Hives Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00220)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	115	2.21		110	2.15		0.59	0.449	0.046
Change from Baseline									
Day 1[c]	115	-0.21	(-7.4%)	110	-0.22	(-8.9%)	0.57	0.954	0.150
Day 2	114	-0.82	(-35.2%)	110	-0.37	(-12.1%)	0.94	<.001	0.424
Day 3	113	-0.94	(-39.2%)	110	-0.44	(-15.2%)	1.02	<.001	0.614
Day 4	113	-0.90	(-41.1%)	108	-0.49	(-21.0%)	0.99	0.003	0.464
Days 1-8	115	-0.88	(-40.8%)	110	-0.44	(-19.9%)	0.83	<.001	0.460
Days 9-15	107	-1.13	(-51.5%)	90	-0.69	(-36.6%)	0.91	0.001	0.175
Days 16-22	103	-1.26	(-56.9%)	83	-0.86	(-43.9%)	0.96	0.006	0.378
Days 23-29	100	-1.29	(-59.5%)	80	-0.93	(-48.5%)	0.94	0.014	0.147
Days 30-36	99	-1.35	(-62.3%)	78	-1.09	(-57.0%)	0.95	0.083	0.601
Days 37-42	96	-1.44	(-65.3%)	73	-1.08	(-56.1%)	0.97	0.020	0.596
Day 1-8	**115**	**-0.88**	**(-40.8%)**	**110**	**-0.44**	**(-19.9%)**	**0.83**	**<.001**	**0.460**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 3 - Size of the Largest Hive Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00220)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	115	2.20		110	2.20		0.62	0.996	0.114
Change from Baseline									
Day 1[c]	115	-0.20	(-5.0%)	110	-0.24	(-8.3%)	0.57	0.608	0.452
Day 2	114	-0.88	(-34.8%)	110	-0.48	(-13.2%)	0.94	0.002	0.166
Day 3	113	-0.98	(-39.9%)	110	-0.48	(-14.2%)	0.95	<.001	0.259
Day 4	113	-0.91	(-38.6%)	108	-0.58	(-20.3%)	0.95	0.011	0.188
Days 1-8	115	-0.90	(-39.0%)	110	-0.52	(-19.3%)	0.81	<.001	0.192
Days 9-15	107	-1.15	(-51.4%)	90	-0.80	(-36.8%)	0.89	0.008	0.031
Days 16-22	103	-1.27	(-56.3%)	83	-0.96	(-44.1%)	0.93	0.028	0.152
Days 23-29	100	-1.29	(-58.3%)	80	-0.97	(-47.7%)	0.93	0.029	0.052
Days 30-36	99	-1.35	(-60.9%)	78	-1.16	(-56.2%)	0.96	0.212	0.306
Days 37-42	96	-1.43	(-64.1%)	73	-1.15	(-54.3%)	0.99	0.076	0.485
Day 1-8	**115**	**-0.90**	**(-39.0%)**	**110**	**-0.52**	**(-19.3%)**	**0.81**	**<.001**	**0.192**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 4 - Pruritus Analysis Results

(All Randomized Subjects) Subject Evaluated AM Now

(Study No. P00220)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	115	1.97		110	2.02		0.60	0.525	0.283
Change from Baseline									
Day 2	111	-0.82	(-36.6%)	110	-0.46	(-14.8%)	0.92	0.005	0.012
Day 3	109	-0.92	(-45.7%)	109	-0.52	(-20.9%)	1.03	0.005	0.253
Day 4	111	-0.96	(-49.0%)	108	-0.61	(-27.4%)	0.98	0.012	0.084
Days 2-8	115	-0.89	(-45.1%)	110	-0.55	(-24.8%)	0.81	0.002	0.076
Days 9-15	107	-1.13	(-56.7%)	90	-0.81	(-37.0%)	0.90	0.016	0.103
Days 16-22	103	-1.11	(-58.5%)	83	-0.95	(-49.0%)	0.87	0.228	0.011
Days 23-29	100	-1.17	(-62.9%)	80	-1.01	(-51.9%)	0.87	0.245	0.003
Days 30-36	99	-1.16	(-62.8%)	78	-1.16	(-61.2%)	0.91	0.958	0.054
Days 37-42	96	-1.24	(-63.0%)	73	-1.22	(-61.2%)	0.91	0.921	0.085
Day 2-8	**115**	**-0.89**	**(-45.1%)**	**110**	**-0.55**	**(-24.8%)**	**0.81**	**0.002**	**0.076**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

Table 5 - Pruritus Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00221)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	95	2.24		94	2.22		0.36	0.695	<.001
Change from Baseline									
Day 1[c]	95	-0.21	(-11.0%)	94	-0.10	(-5.3%)	0.56	0.176	0.460
Day 2	95	-0.94	(-45.2%)	94	-0.30	(-14.0%)	0.81	<.001	0.005
Day 3	95	-1.09	(-50.2%)	93	-0.32	(-14.2%)	0.82	<.001	0.006
Day 4	95	-1.26	(-57.4%)	91	-0.62	(-25.6%)	0.80	<.001	<.001
Days 1-8	95	-1.22	(-56.0%)	94	-0.49	(-21.5%)	0.67	<.001	0.004
Days 9-15	89	-1.53	(-69.3%)	76	-0.79	(-34.1%)	0.75	<.001	0.010
Days 16-22	81	-1.59	(-70.5%)	69	-0.91	(-40.7%)	0.83	<.001	0.058
Days 23-29	79	-1.66	(-74.9%)	67	-1.00	(-46.8%)	0.78	<.001	0.253
Days 30-36	77	-1.64	(-73.9%)	62	-1.07	(-49.2%)	0.78	<.001	0.164
Days 37-42	77	-1.63	(-74.0%)	62	-1.07	(-48.7%)	0.79	<.001	0.039
Day 1-8	**95**	**-1.22**	**(-56.0%)**	**94**	**-0.49**	**(-21.5%)**	**0.67**	**<.001**	**0.004**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 6 - Number of Hives Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00221)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	95	2.22		94	2.14		0.70	0.434	0.780
Change from Baseline									
Day 1[c]	95	-0.20	(-11.0%)	94	-0.06	(-4.0%)	0.55	0.086	0.840
Day 2	95	-0.73	(-37.4%)	94	-0.11	(-6.5%)	0.86	<.001	0.370
Day 3	95	-0.92	(-45.1%)	93	-0.25	(-11.2%)	0.95	<.001	0.497
Day 4	95	-0.97	(-45.4%)	91	-0.48	(-20.8%)	0.93	<.001	0.010
Days 1-8	95	-0.98	(-48.4%)	94	-0.33	(-15.8%)	0.80	<.001	0.264
Days 9-15	89	-1.24	(-61.0%)	76	-0.58	(-26.3%)	0.92	<.001	0.561
Days 16-22	81	-1.31	(-61.3%)	69	-0.70	(-33.3%)	0.99	<.001	0.759
Days 23-29	79	-1.38	(-66.9%)	67	-0.82	(-41.0%)	0.94	<.001	0.957
Days 30-36	77	-1.27	(-62.9%)	62	-0.83	(-42.1%)	0.97	0.011	0.844
Days 37-42	77	-1.30	(-63.9%)	62	-0.78	(-37.3%)	1.03	0.005	0.768
Day 1-8	**95**	**-0.98**	**(-48.4%)**	**94**	**-0.33**	**(-15.8%)**	**0.80**	**<.001**	**0.264**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 7 - Size of the Largest Hive Analysis Results

(All Randomized Subjects) Subject Evaluated Mean AM/PM Prior 12 Hrs

(Study No. P00221)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	95	2.18		94	2.15		0.68	0.752	0.733
Change from Baseline									
Day 1[c]	95	-0.24	(-10.2%)	94	-0.11	(-5.1%)	0.56	0.142	0.796
Day 2	95	-0.75	(-40.8%)	94	-0.12	(-7.8%)	0.80	<.001	0.055
Day 3	95	-1.01	(-49.5%)	93	-0.25	(-12.3%)	0.84	<.001	0.060
Day 4	95	-0.94	(-45.7%)	91	-0.46	(-23.6%)	0.87	<.001	0.003
Days 1-8	95	-0.97	(-49.7%)	94	-0.32	(-17.0%)	0.73	<.001	0.026
Days 9-15	89	-1.21	(-60.9%)	76	-0.59	(-25.6%)	0.89	<.001	0.213
Days 16-22	81	-1.29	(-61.4%)	69	-0.76	(-35.6%)	0.97	0.002	0.769
Days 23-29	79	-1.33	(-65.2%)	67	-0.84	(-41.8%)	0.93	0.002	0.869
Days 30-36	77	-1.27	(-62.6%)	62	-0.82	(-41.7%)	0.94	0.010	0.699
Days 37-42	77	-1.34	(-65.3%)	62	-0.78	(-37.0%)	1.02	0.003	0.845
Day 1-8	**95**	**-0.97**	**(-49.7%)**	**94**	**-0.32**	**(-17.0%)**	**0.73**	**<.001**	**0.026**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

c: Day 1 includes PM score only.

Table 8 - Pruritus Analysis Results

(All Randomized Subjects) Subject Evaluated AM Now

(Study No. P00221)

	DL 5.0 mg QD			Placebo			Analysis		
		LS	(Mean %		LS	(Mean %		Model P-values	
Interval	N	Mean[a]	Change)[b]	N	Mean	Change)	Pstd[a]	Trt	Site
Baseline	95	1.99		94	2.11		0.57	0.140	0.003
Change from Baseline									
Day 2	95	-0.86	(-45.1%)	93	-0.18	(-3.5%)	0.92	<.001	0.036
Day 3	95	-0.89	(-49.3%)	92	-0.15	(-3.3%)	0.94	<.001	0.016
Day 4	95	-0.96	(-50.0%)	91	-0.53	(-20.8%)	0.96	0.003	0.004
Days 2-8	95	-1.05	(-55.1%)	94	-0.41	(-14.5%)	0.77	<.001	0.009
Days 9-15	89	-1.27	(-64.9%)	76	-0.69	(-26.7%)	0.83	<.001	0.008
Days 16-22	81	-1.34	(-64.9%)	69	-0.85	(-36.8%)	0.92	0.002	0.066
Days 23-29	79	-1.39	(-70.8%)	67	-0.96	(-45.1%)	0.87	0.004	0.224
Days 30-36	77	-1.37	(-70.5%)	62	-0.97	(-44.8%)	0.87	0.010	0.310
Days 37-42	77	-1.36	(-68.9%)	62	-1.02	(-46.0%)	0.89	0.033	0.094
Day 2-8	**95**	**-1.05**	**(-55.1%)**	**94**	**-0.41**	**(-14.5%)**	**0.77**	**<.001**	**0.009**

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with Treatment and site effects.

b: Mean percent changes are raw means.

/s/

James Gebert
4/4/01 01:28:40 PM
BIOMETRICS

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4/11/01 04:42:42 PM
BIOMETRICS