

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Day 2-8	-3.52 (-19.7 %)	-4.59 (-25.7 %)	-5.30 (-28.9 %)	0.04	<0.01
Day 9-15	-4.52 (-25.6 %)	-5.57 (-31.2 %)	-6.32 (-34.3 %)	0.10	<0.01
Day 2	-3.10 (-17.0 %)	-3.78 (-21.5 %)	-4.32 (-23.5 %)	0.21	0.02
Day 3	-3.21 (-18.0 %)	-4.56 (-25.8 %)	-5.23 (-28.2 %)	0.02	<0.01
Day 4	-3.45 (-19.4 %)	-4.68 (-26.2 %)	-5.41 (-29.6 %)	0.03	<0.01
Total symptom score (including cough), AM prior 12 hours reflective					
Day 2-15	-3.60 (-20.0 %)	-4.65 (-26.6 %)	-5.33 (-29.6 %)	0.05	<0.01
Day 2-8	-3.17 (-17.2 %)	-4.25 (-24.3 %)	-4.90 (-27.3 %)	0.04	<0.01
Day 9-15	-4.12 (-23.4 %)	-5.10 (-29.1 %)	-5.86 (-32.5 %)	0.13	<0.01
Day 2	-2.59 (-13.3 %)	-2.84 (-16.6 %)	-3.54 (-19.7 %)	0.65	0.09
Day 3	-2.53 (-13.0 %)	-4.11 (-23.6 %)	-4.76 (-25.7 %)	<0.01	<0.01
Day 4	-3.11 (-16.9 %)	-4.20 (-24.3 %)	-4.76 (-26.3 %)	0.07	<0.01
Total symptom score (including cough), AM instantaneous					
Day 2-15	-3.72 (-19.9 %)	-4.66 (-25.4 %)	-5.03 (-27.6 %)	0.09	0.02
Day 2-8	-3.18 (-16.9 %)	-4.21 (-22.8 %)	-4.65 (-25.9 %)	0.15	<0.01
Day 9-15	-4.39 (-23.7 %)	-5.20 (-28.6 %)	-5.52 (-30.0 %)	0.21	0.08
Day 2	-2.35 (-11.6 %)	-3.25 (-16.9 %)	-3.28 (-18.5 %)	0.11	0.10
Day 3	-2.48 (-13.0 %)	-4.00 (-22.0 %)	-4.58 (-25.0 %)	0.01	<0.01
Day 4	-3.05 (-16.0 %)	-4.08 (-22.0 %)	-4.40 (-24.3 %)	0.09	0.02
Total nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-1.80 (20.4 %)	-2.27 (-24.9 %)	-2.67 (-29.3 %)	0.06	<0.01
Total non-nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-2.13 (-23.6 %)	-2.75 (-31.5 %)	-3.05 (-32.8 %)	0.04	<0.01
Rhinorrhea, AM + PM prior 12 hours reflective					
Day 2-15	-0.49 (-19.9 %)	-0.57 (-22.9 %)	-0.67 (-27.2 %)	0.19	<0.01
Nasal congestion, AM + PM prior 12 hours reflective					
Day 2-15	-0.45 (-18.2 %)	-0.52 (-20.1 %)	-0.59 (-22.6 %)	0.25	0.03
Nasal itching, AM + PM prior 12 hours reflective					
Day 2-15	-0.44 (-19.9 %)	-0.57 (-24.6 %)	-0.65 (-28.1 %)	0.07	<0.01
Sneezing, AM + PM prior 12 hours reflective					
Day 2-15	-0.43 (-19.9 %)	-0.60 (-30.2 %)	-0.76 (-33.6 %)	0.02	<0.01
Itchy or burning eyes, reflective					
Day 2-15	-0.48 (-23.4 %)	-0.62 (-29.5 %)	-0.64 (-32.4 %)	0.05	<0.01
Tearing, AM + PM prior 12 hours reflective					
Day 2-15	-0.44 (-23.9 %)	-0.60 (-32.9 %)	-0.5 (-16.2 %)	0.03	0.02
Redness of eyes, AM + PM prior 12 hours reflective					
Day 2-15	-0.37 (-20.1 %)	-0.55 (-27.7 %)	-0.56 (-29.0 %)	0.02	0.01
Itchy ears or palate, AM + PM prior 12 hours reflective					
Day 2-15	-0.43 (-16.0 %)	-0.52 (-29.1 %)	-0.67 (-34.9 %)	0.20	<0.01
Cough, reflective					
Day 2-15	-0.42 (-18.3 %)	-0.45 (-31.7 %)	-0.50 (-31.8 %)	0.69	0.28
Overall condition of SAR, joint patient and physician score					
Day 4	-0.49 (-17.2 %)	-0.55 (-19.7 %)	-0.67 (-25.0 %)	0.44	0.02
Day 8	-0.50 (-18.3 %)	-0.69 (-25.9 %)	-0.73 (-27.4 %)	0.03	<0.01
Day 15	-0.60 (-23.0 %)	-0.65 (-23.5 %)	-0.69 (-25.1 %)	0.66	0.36

Source: vol 124, p 56-69, 299, 335

C98-224: Multi-dose two-week efficacy and safety study

This was replicate of study C98-223 also conducted in 10 US centers during the fall allergy season of 1998. The study design, efficacy, and safety parameters of the two studies were identical. Patient demographics of the two studies were similar. A total of 492 patients were randomized, 164 to each of the three groups. Over 90% of the patients completed the study. The ITT population included 489 patients. A total of 425 (86%) patients were at least 18 years of age, of these 422 (99%) completed QOL assessment.

Results of change from baseline in the patient assessed AM plus PM total reflective symptoms score averaged over the 2-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 11. With the larger dose failing to show efficacy and the smaller dose showing efficacy, it is difficult to place much weight on this study. Given this limitation, this study supports the DCL 5 mg dose based on the protocol specified primary efficacy variable. As in study C98-223, there was a large placebo response at the second week of treatment, however, DCL treatment also had a larger effect size at the second week. For DCL 5mg dose, efficacy was not seen by day 4. Analyses of individual symptom score show larger effect sizes for sneezing, and itching of eyes and nose. These are typical histamine mediated symptoms. QOL measures shows trends favoring DCL for some domains; however, none of the differences were statistically significant (data not shown). All doses of DCL were well tolerated in the study. Dry mouth was reported by 1%, 5%, and 2% of placebo, DCL 5 mg, and DCL 7.5 mg treated patients, respectively. Somnolence was reported by 2%, 2%, and 1% of placebo, DCL 5 mg, and DCL 7.5 mg treated patients, respectively. QT interval did not change meaningfully on treatment. This study supports the DCL 5 mg dose, however, the support is not convincing because of inverse dose-ordering.

Table 11. Mean change from baseline in various efficacy measures

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Total symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-4.23 (-21.8 %)	-5.57 (-30.4 %)	-4.45 (-23.8 %)	0.02	0.68
Day 2-8	-3.95 (-20.5 %)	-5.09 (-27.7 %)	-4.30 (-22.9 %)	0.03	0.50
Day 9-15	-4.65 (-23.9 %)	-6.35 (-34.6 %)	-4.60 (-24.9 %)	<0.01	0.94
Day 2	-3.22 (-16.3 %)	-4.05 (-22.0 %)	-4.01 (-21.1 %)	0.14	0.16
Day 3	-3.99 (-20.6 %)	-4.91 (-26.9 %)	-4.53 (-24.3 %)	0.13	0.37
Day 4	-4.14 (-21.5 %)	-5.29 (-28.9 %)	-4.56 (-24.2 %)	0.06	0.50
Total symptom score (including cough), AM prior 12 hours reflective					
Day 2-15	-4.15 (-21.5 %)	-5.36 (-29.8 %)	-4.26 (-22.8 %)	0.03	0.84
Day 2-8	-3.87 (-20.0 %)	-4.89 (-27.1 %)	-4.18 (-22.2 %)	0.06	0.57
Day 9-15	-4.57 (-23.6 %)	-5.93 (-33.0 %)	-4.30 (-23.4 %)	0.04	0.67
Day 2	-2.74 (-13.4 %)	-3.21 (-17.4 %)	-3.37 (-17.6 %)	0.43	0.29
Day 3	-3.92 (-19.9 %)	-4.40 (-24.5 %)	-4.34 (-23.3 %)	0.45	0.52
Day 4	-3.80 (-19.4 %)	-4.74 (-26.5 %)	-4.46 (-23.1 %)	0.15	0.32
Total symptom score (including cough), AM instantaneous					
Day 2-15	-3.76 (-19.4 %)	-4.96 (-26.7 %)	-4.08 (-22.4 %)	0.03	0.55
Day 2-8	-3.64 (-18.9 %)	-4.51 (-24.0 %)	-3.97 (-21.6 %)	0.10	0.54
Day 9-15	-4.03 (-20.6 %)	-5.53 (-29.9 %)	-4.12 (-23.0 %)	0.02	0.89
Day 2	-2.98 (-15.5 %)	-3.27 (-17.1 %)	-3.04 (-16.0 %)	0.60	0.91
Day 3	-3.31 (-16.9 %)	-4.29 (-22.8 %)	-4.00 (-21.7 %)	0.12	0.28
Day 4	-3.32 (-17.5 %)	-4.45 (-23.6 %)	-4.15 (-22.2 %)	0.06	0.17

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Total nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-1.97 (-20.8 %)	-2.58 (-28.1 %)	-2.15 (-22.8 %)	0.02	0.50
Total non-nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-2.25 (-22.5 %)	-2.99 (-32.7 %)	-2.31 (-24.7 %)	0.02	0.84
Rhinorrhea, AM + PM prior 12 hours reflective					
Day 2-15	-0.56 (-21.7 %)	-0.65 (-25.9 %)	-0.54 (-21.2 %)	0.19	0.82
Nasal congestion, AM + PM prior 12 hours reflective					
Day 2-15	-0.49 (-19.3 %)	-0.57 (-23.3 %)	-0.45 (-16.8 %)	0.27	0.55
Nasal itching, AM + PM prior 12 hours reflective					
Day 2-15	-0.47 (-18.4 %)	-0.65 (-28.6 %)	-0.59 (-23.0 %)	0.03	0.14
Sneezing, AM + PM prior 12 hours reflective					
Day 2-15	-0.45 (-19.0 %)	-0.71 (-34.9 %)	-0.57 (-25.8 %)	<0.01	0.12
Itchy or burning eyes, reflective					
Day 2-15	-0.51 (-20.4 %)	-0.67 (-32.1 %)	-0.52 (-24.6 %)	0.03	0.84
Tearing, AM + PM prior 12 hours reflective					
Day 2-15	-0.47 (-18.0 %)	-0.61 (-29.6 %)	-0.51 (-25.7 %)	0.07	0.59
Redness of eyes, AM + PM prior 12 hours reflective					
Day 2-15	-0.40 (-19.0 %)	-0.55 (-29.8 %)	-0.43 (-23.6 %)	0.04	0.63
Itchy ears or palate, AM + PM prior 12 hours reflective					
Day 2-15	-0.49 (-18.2 %)	-0.64 (-33.5 %)	-0.47 (-19.0 %)	0.05	0.81
Cough, reflective					
Day 2-15	-0.37 (-14.9 %)	-0.50 (-33.2 %)	-0.37 (-15.3 %)	0.09	1.00
Overall condition of SAR, joint patient and physician score					
Day 4	-0.47 (-15.8 %)	-0.56 (-20.1 %)	-0.48 (-17.3 %)	0.26	0.84
Day 8	-0.56 (-19.2 %)	-0.68 (-24.1 %)	-0.47 (-17.1 %)	0.19	0.36
Day 15	-0.55 (-19.0 %)	-0.74 (-27.9 %)	-0.60 (-22.8 %)	0.04	0.59

Source: vol 127, p 56-72, 295,

C98-225: Multi-dose four-week efficacy and safety study

This was also replicate of studies C98-223 and C98-224 also conducted in 10 US centers during the fall allergy season of 1998. The study design, efficacy, and safety parameters of the two studies were similar, except this study had treatment duration of 4 weeks. However, the two studies were similar, except this study had treatment duration of 4 weeks. However, protocol specified primary efficacy variable was assessed at 2 weeks, which is same as studies C98-223 and C98-224. Demographics of patients enrolled in this study were similar to the previous two studies. A total of 475 patients were randomized, 158 to placebo, 147 to DCL 5 mg, and 159 to DCL 7.5 mg. Over 90% of the patients completed the study. ITT population included 474 patients. A total of 407 (86%) patients were at least 18 years of age, of these 397 (98%) completed QOL assessment.

Results of change from baseline in the patient assessed AM plus PM total reflective symptoms score averaged over the 2-week treatment period (primary efficacy variable), and other efficacy measures are shown in Table 12. Based on the protocol specified primary efficacy variable, the results show efficacy for the 7.5 mg dose but not for the 5 mg dose. QOL measures shows trends favoring DCL for some domains; however, none of the differences were statistically significant (data not shown). All doses of DCL were well tolerated in the study. Dry mouth was reported by 4%, 5%, and 5% of placebo, DCL 5 mg, and DCL 7.5 mg treated patients, respectively. Somnolence was reported by 4%, 3%, and

2% of placebo, DCL 5 mg, and DCL 7.5 mg treated patients, respectively. QT interval did not change meaningfully on treatment. This study supports the DCL 7.5 mg dose, but not the DCL 5 mg dose.

Table 12. Mean change from baseline in various efficacy measures

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Total symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-4.15 (-22.4 %)	-4.63 (-24.8 %)	-5.22 (-28.1 %)	0.35	0.04
Day 2-8	-3.68 (-19.6 %)	-4.44 (-23.6 %)	-4.77 (-25.5 %)	0.13	0.03
Day 9-15	-4.65 (-25.2 %)	-4.86 (-26.3 %)	-5.84 (-31.4 %)	0.73	0.05
Day 16-22	-5.39 (-28.2 %)	-5.63 (-30.2 %)	-6.26 (-33.6 %)	0.71	0.18
Day 23-29	-6.00 (-31.9 %)	-6.23 (-33.1 %)	-6.38 (-34.6 %)	0.74	0.58
Day 2	-2.50 (-12.8 %)	-3.84 (-20.4 %)	-4.05 (-21.4 %)	0.01	<0.01
Day 3	-3.21 (-16.5 %)	-4.54 (-24.6 %)	-4.54 (-23.8 %)	0.02	0.02
Day 4	-3.79 (-20.3 %)	-4.60 (-24.8 %)	-4.63 (-24.8 %)	0.15	0.14
Total symptom score (including cough), AM prior 12 hours reflective					
Day 2-15	-3.85 (-21.0 %)	-4.08 (-22.1 %)	-4.80 (-26.0 %)	0.66	0.07
Day 2-8	-3.40 (-18.4 %)	-3.82 (-20.2 %)	-4.36 (-23.5 %)	0.42	0.07
Day 9-15	-4.33 (-23.6 %)	-4.37 (-24.1 %)	-5.37 (-29.0 %)	0.95	0.09
Day 16-22	-5.09 (-26.8 %)	-5.09 (-27.5 %)	-5.72 (-30.9 %)	1.00	0.35
Day 23-29	-5.71 (-30.9 %)	-5.72 (-30.8 %)	-5.88 (-32.2 %)	1.00	0.81
Day 2	-2.16 (-10.8 %)	-2.68 (-13.5 %)	-3.37 (-18.0 %)	0.34	0.03
Day 3	-2.67 (-13.6 %)	-3.66 (-19.5 %)	-3.93 (-20.2 %)	0.10	0.04
Day 4	-3.59 (-19.2 %)	-3.89 (-21.0 %)	-4.02 (-21.2 %)	0.63	0.48
Total symptom score (including cough), AM instantaneous					
Day 2-15	-3.88 (-20.7 %)	-3.99 (-20.9 %)	-4.80 (-26.0 %)	0.85	0.06
Day 2-8	-3.56 (-18.8 %)	-3.87 (-19.9 %)	-4.36 (-23.5 %)	0.55	0.07
Day 9-15	-4.20 (-22.3 %)	-4.14 (-21.9 %)	-5.37 (-29.0 %)	0.92	0.06
Day 16-22	-5.16 (-26.7 %)	-4.76 (-25.1 %)	-5.72 (-30.9 %)	0.55	0.34
Day 23-29	-5.76 (-30.3 %)	-5.33 (-27.7 %)	-5.88 (-32.2 %)	0.55	0.65
Day 2	-2.72 (-14.1 %)	-2.54 (-13.2 %)	-3.37 (-18.0 %)	0.75	0.05
Day 3	-2.96 (-15.2 %)	-3.81 (-19.6 %)	-3.93 (-20.2 %)	0.15	0.04
Day 4	-3.58 (-18.9 %)	-3.97 (-21.0 %)	-4.02 (-21.2 %)	0.52	0.13
Total nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-1.86 (-20.3 %)	-2.05 (-21.4 %)	-2.38 (-25.6 %)	0.44	0.03
Total non-nasal symptom score (including cough), AM + PM prior 12 hours reflective					
Day 2-15	-2.28 (-24.4 %)	-2.58 (-28.5 %)	-2.84 (-30.5 %)	0.31	0.06
Rhinorrhea, AM + PM prior 12 hours reflective					
Day 2-15	-0.49 (-19.2 %)	-0.48 (-18.5 %)	-0.57 (-22.9 %)	0.94	0.21
Nasal congestion, AM + PM prior 12 hours reflective					
Day 2-15	-0.45 (-17.9 %)	-0.49 (-18.2 %)	-0.56 (-22.0 %)	0.55	0.08
Nasal itching, AM + PM prior 12 hours reflective					
Day 2-15	-0.47 (-21.4 %)	-0.54 (-22.6 %)	-0.66 (-27.6 %)	0.31	0.01
Sneezing, AM + PM prior 12 hours reflective					
Day 2-15	-0.46 (-19.3 %)	-0.54 (-23.7 %)	-0.60 (-28.9 %)	0.26	0.05
Itchy or burning eyes, reflective					
Day 2-15	-0.48 (-22.1 %)	-0.57 (-27.8 %)	-0.65 (-30.1 %)	0.19	0.02
Tearing, AM + PM prior 12 hours reflective					
Day 2-15	-0.53 (-27.0 %)	-0.55 (-30.6 %)	-0.61 (-30.0 %)	0.76	0.26
Redness of eyes, AM + PM prior 12 hours reflective					
Day 2-15	-0.46 (-23.9 %)	-0.49 (-24.4 %)	-0.57 (-30.4 %)	0.73	0.12

Measures Time	Placebo	DCL 5 mg	DCL 7.5 mg	p-value, placebo vs	
				DCL 5 mg	DCL 7.5 mg
Itchy ears or palate, AM + PM prior 12 hours reflective					
Day 2-15	-0.45 (-22.6 %)	-0.51 (-25.6 %)	-0.58 (-26.5 %)	0.43	0.08
Cough, reflective					
Day 2-15	-0.36 (-11.3 %)	-0.46 (-19.2 %)	-0.44 (-19.1 %)	0.18	0.28
Overall condition of SAR, joint patient and physician score					
Day 4	-0.41 (-13.2 %)	-0.56 (-19.1 %)	-0.64 (-22.6 %)	0.08	0.07
Day 8	-0.48 (-15.3 %)	-0.64 (-22.0 %)	-0.72 (-26.0 %)	0.08	0.10
Day 15	-0.54 (-18.7 %)	-0.60 (-21.5 %)	-0.62 (-22.0 %)	0.52	0.35
Day 29	-0.67 (-22.6 %)	-0.74 (-26.8 %)	-0.75 (-26.3 %)	0.42	0.37

Source: vol 130, p 58-72, 288

C98-226: Day-in-the park onset of action study

This was a single dose, two-arm, 1:1 randomized, double-blind, placebo-controlled, one-day park study that evaluated the onset of action of DCL 5 mg versus placebo. Onset of action was defined as the first time point that DCL was statistically superior to placebo in change from baseline in total symptom score that continued to be statistically superior to placebo for subsequent time points. Total symptom score included four nasal symptoms (rhinorrhea, congestion, itching, and sneezing) and four non-nasal symptoms (itchy eyes, tearing, itchy ears or palate, and cough) scored on 4-point scale. The study was conducted on ~~12 to 65-year~~ old (overall mean age 31 year) patients with SAR in two US centers during the fall allergy season of 1998. Patients were screened at least one week prior to the study day. On the study day patients were in a designated outdoor park. Study drug was administered at about 8:30 AM. Patients scored symptoms 60 minutes and immediately before dosing, and after dosing every 15 minutes for the first 2 hours, and every 30 minutes for hours 3, 4, and 5.

A total of 310 patients were randomized, 155 to each treatment group. All patients were in the ITT group. Change in total symptom score for selected time points are shown in Table 13. Scores decreased over time in both treatment groups. There are no statistically significant differences between the treatment groups, indicating that an onset of action was not demonstrated in this study. Analyses of data without congestion and cough score did not change the conclusion (data not shown).

Table 13. Mean change from baseline in total symptom score

Time	Placebo (n=155)	DCL 5 mg (n=155)	P value, Pbo vs DCL
Baseline	19.36	19.66	
Change from baseline:			
15 minutes	-1.81 (-9.4 %)	-1.61 (-8.3 %)	0.547
30 minutes	-3.33 (-17.0 %)	-2.73 (-17.0 %)	0.156
45 minutes	-4.30 (-22.0 %)	-4.18 (-21.9 %)	0.808
1 hour	-5.00 (-25.6 %)	-4.93 (-25.6 %)	0.894
2 hour	-6.99 (-35.7 %)	-6.99 (-36.0 %)	0.992
3 hour	-7.65 (-39.1 %)	-8.25 (-42.4 %)	0.391
4 hour	-8.48 (-43.8 %)	-9.25 (-47.3 %)	0.277
5 hour	-8.90 (-45.5 %)	-9.99 (-51.2 %)	0.142

Source: vol 133, p 42

198-367: Environmental exposure unit (EEU) onset of action study

This was a single-dose, three-arm, 1:1:1 randomized, double-blind, placebo-controlled, parallel-group study that evaluated the onset of action of DCL 5 mg and DCL 7.5 mg versus placebo while exposed to ragweed pollen in an EEU. The study was conducted on 16 to 65 year old (mean age 32 year) patients with SAR in a single center in Ontario, Canada, in November 1988. The study had a screening visit, priming visits (up to six 3-hour priming in EEU) 1 to 14 days before treatment, and a treatment day. On the treatment day, patients arrived in the EEU at 8 AM, and scored symptoms every 30 minutes until 9:30 AM. Sufficiently symptomatic patients were treated at 10 AM, and they scored symptoms every 15 minutes for the first 2 hours, and every 30 minutes for hours 3, 4, and 5. Definition of onset of action was same as the day-in-the-park onset of action study.

A total of 360 patients were randomized, 120 to each treatment group. All completed the study. Change in total symptom score for selected time points are shown in Table 14. Onset of action for DCL 5 mg was 3 hours, and 2 hours when cough was excluded. Onset of action for DCL 7.5 mg was 3 hours and 30 minutes. Onset of action for DCL 7.5 mg did not change when cough was excluded. Results of analyses excluding both cough and congestion were the same as those excluding cough alone.

Table 14. Mean change from baseline in total symptom score

Time	Placebo (n=120)	DCL 5 mg (n=120)	DCL 7.5 mg (n=120)	P value, placebo versus	
				DCL 5 mg	DCL 7.5 mg
Baseline	19.24	19.03	18.86		
Change from baseline:					
15 minutes	-1.20 (-5.9 %)	-1.26 (-6.4 %)	-0.74 (-3.7 %)	0.85	0.13
30 minutes	-3.12 (-15.9 %)	-3.30 (-17.6 %)	-3.04 (-15.9 %)	0.70	0.87
1 hour	-5.85 (-30.5 %)	-6.29 (-33.1 %)	-6.17 (-32.7 %)	0.50	0.63
1 hour 30 minutes	-7.43 (-38.8 %)	-8.22 (-43.3 %)	-7.88 (-41.4 %)	0.30	0.55
2 hour	-8.08 (-42.2 %)	-9.46 (-49.8 %)	-8.71 (-45.9 %)	0.08	0.43
2 hour 30 minutes	-8.07 (-41.9 %)	-9.54 (-50.6 %)	-9.21 (-48.7 %)	0.06	0.15
3 hour	-8.34 (-43.2 %)	-10.1 (-53.9 %)	-9.52 (-50.3 %)	0.03	0.14
3 hour 30 minutes	-8.05 (-41.3 %)	-10.2 (-54.6 %)	-9.68 (-51.3 %)	<0.01	0.05
4 hour	-7.73 (-39.9 %)	-10.3 (-55.1 %)	-9.67 (-51.7 %)	<0.01	0.02
4 hour 30 minutes	-7.34 (-37.8 %)	-10.3 (-54.9 %)	-9.42 (-50.4 %)	<0.01	0.01
5 hour	-6.95 (-35.8 %)	-10.1 (-53.5 %)	-9.53 (-51.0 %)	<0.01	<0.01

Source: vol 135, p 42

198-448: Environmental exposure unit (EEU) onset of action study

This was a single-dose, double-blind, placebo-controlled, three-way cross-over study that evaluated the onset of action of DCL 5 mg and DCL 7.5 mg versus placebo while exposed to grass pollen in an EEU. The study was conducted on 19 to 42 year old (mean age 26.5 year) patients with SAR in a single center in Vienna, Austria, between October and December 1988. The study had a screening visit, followed by three treatment visits separated by at least 10 days washout period in between. On the treatment day, patients scored symptoms 2 and 1 hour before dosing. Sufficiently symptomatic patients were then given the study drug, and then they scored symptoms every 15 minutes for the first 2 hours, and every 30 minutes for

hours 3, 4, and 5. Definition of onset of action was same as the day-in-the-park onset of action study.

A total of 60 patients were randomized of which 53 completed the three treatment periods. Change in total symptom score for selected time points are shown in Table 15. Onset of action for DCL 5 mg was 1 hour and 15 minutes, and for DCL 7.5 mg was 3 hours and 30 minutes. Results of analyses excluding cough and congestion were the same as those including cough and congestion.

Table 15. Mean change from baseline in total symptom score

Time	Placebo (n=120)	DCL 5 mg (n=120)	DCL 7.5 mg (n=120)	P value, versus placebo	
				DCL 5 mg	DCL 7.5 mg
Baseline	15.75	15.79	15.49		
Change from baseline:					
15 minutes	-0.68 (-4.3 %)	-0.87 (-5.5 %)	-0.66 (-3.9 %)	0.52	0.97
30 minutes	-2.19 (-13.7 %)	-2.09 (-12.9 %)	-1.60 (-10.3 %)	0.81	0.20
1 hour	-4.51 (-28.4 %)	-4.94 (-31.2 %)	-3.70 (-24.3 %)	0.43	0.10
1 hour 15 minutes	-4.81 (-30.6 %)	-6.00 (-37.9 %)	-4.77 (-31.3 %)	0.03	0.95
1 hour 30 minutes	-4.98 (-31.7 %)	-6.42 (-40.9 %)	-5.49 (-36.0 %)	0.02	0.37
1 hour 45 minutes	-5.09 (-31.8 %)	-6.74 (-42.7 %)	-5.91 (-38.8 %)	<0.01	0.17
2 hour	-5.23 (-33.0 %)	-6.83 (-43.3 %)	-6.11 (-40.5 %)	0.02	0.17
2 hour 30 minutes	-4.98 (-31.6 %)	-7.43 (-47.1 %)	-6.51 (-42.5 %)	<0.01	0.02
3 hour	-5.66 (-35.9 %)	-7.91 (-50.0 %)	-6.87 (-45.4 %)	<0.01	0.09
3 hour 30 minutes	-5.04 (-31.4 %)	-7.91 (-50.0 %)	-7.21 (-47.3 %)	<0.01	<0.01
4 hour	-4.45 (-27.6 %)	-7.66 (-48.5 %)	-7.09 (-46.7 %)	<0.01	<0.01
4 hour 30 minutes	-4.47 (-27.5 %)	-7.68 (-48.7 %)	-7.06 (-46.4 %)	<0.01	0.01
5 hour	-4.15 (-25.6 %)	-7.66 (-48.7 %)	-7.06 (-46.3 %)	<0.01	<0.01

Source: vol 137, p 44

P-00287: Environmental exposure unit (EEU) onset of action study

This was a single-dose, double-blind, placebo-controlled, two-way cross-over study that evaluated the onset of action of DCL 5 mg versus placebo while exposed to grass pollen in an EEU. The study was conducted on 19 to 42 year old (mean age 25.4 year) patients with SAR in a single center in Vienna, Austria, between March and April 1999. The study had a screening visit, followed by three treatment visits separated by at least 10 days washout period in between. On the treatment day, patients scored symptoms 2 and 1 hour before dosing. Sufficiently symptomatic patients were then given the study drug, and then they scored symptoms every 15 minutes for the first 2 hours, and every 30 minutes for hours 3, 4, and 5. Definition of onset of action was same as the day-in-the-park onset of action study.

A total of 53 patients were randomized of which 52 completed the two treatment periods. Change in total symptom score for selected time points are shown in Table 16. Onset of action for DCL 5 mg was 1 hour and 45 minutes. Results of analyses excluding cough and congestion were the similar as those including cough and congestion.

Table 16. Mean change from baseline in total symptom score

Time	Placebo (n=52)	DCL 5 mg (n=52)	P value, Pbo vs DCL
Baseline	15.52	15.35	
Change from baseline:			
15 minutes	-0.38 (-2.2 %)	-0.73 (-4.6 %)	0.20
30 minutes	-1.56 (-9.8 %)	-1.92 (-12.9 %)	0.38
1 hour	-3.19 (-20.5 %)	-3.23 (-21.9 %)	0.94
1 hour 45 minutes	-3.85 (-25.0 %)	-5.12 (-34.0 %)	0.04
2 hour	-3.88 (-25.3 %)	-5.42 (-35.8 %)	0.01
3 hour	-4.19 (-27.3 %)	-6.23 (-41.2 %)	<0.01
4 hour	-4.12 (-26.6 %)	-6.12 (-40.4 %)	<0.01
5 hour	-3.94 (-25.1 %)	-6.17 (-40.7 %)	<0.01

Source: vol 139, p 41

Efficacy assessment

Efficacy of DCL 5 mg QD dose is supported by the submitted data reviewed above. Efficacy of DCL was assessed primarily by patient scoring of total symptom scores that included four nasal symptoms (rhinorrhea, congestion, itching, and sneezing), and four or five non-nasal symptoms (itchy or burning eyes, tearing, redness of eyes, sneezing, and cough) in a dose-ranging study, and three phase 3 efficacy and safety studies. Based on the protocol specified primary efficacy endpoint (change from baseline in the patient assessed AM plus PM total reflective symptom score averaged over 2-week treatment period), the submitted data support efficacy for both DCL 5 mg and DCL 7.5 mg QD doses. Effect sizes for both doses compared to placebo were small (about 6-16% over placebo on primary endpoint in studies where active treatment were statistically superior to placebo), and dose ordering between the two doses were not consistently seen in the clinical studies. The sponsor has correctly selected the lowest effective dose for marketing approval. DCL 5 mg dose is specifically supported by the dose-ranging study C98-001, and study C98-223. Study C98-224 could also be taken to support the 5 mg dose, however, the inverse dose-ordering between 5 and 7.5 mg doses was problematic. The sponsor therefore has two well-controlled studies that satisfy the regulatory requirement for approval of the DCL 5mg QD dose. Further, the PK study P000117 has shown that DCL 5 mg QD and loratadine 10 mg QD gives comparable systemic exposure of DCL. Loratadine 10 mg QD is approved for treatment of SAR symptoms.

DPADP's preferred method of assessing efficacy of allergic rhinitis drugs is patient recording of instantaneous, rather than reflective, symptom scores, because instantaneous scoring captures end of dosing interval efficacy. The sponsor has obtained instantaneous scores in all efficacy studies. The instantaneous scores were numerically superior for DCL 5 mg and DCL 7.5 mg doses compared to placebo, although the differences were not statistically significant. The studies were not powered to show such statistical differences. These positive trends further support efficacy.

Onset of action was looked at in the phase 3 studies, and specifically addressed in one day-in-the-park study, and in three EEU studies. In the phase 3 studies statistically significant separation between DCL 5 mg and placebo for scores used in primary efficacy variable analyses occurred at day 2 onwards in study C98-001, and day 3 onwards in study C98-223. Studies C98-224 and C98-225 failed to show a consistent separation between DCL 5 mg and

placebo arms. The day-in-the park study C98-226 failed to show an onset of action at all, presumably because of large placebo response. In the two EEU onset of action studies that compared the DCL 5 mg and 7.5 mg doses, onset of action was faster for the 5 mg dose compared to the 7.5 mg dose. This reverse dose ordering is difficult to explain. Given the variable and inconsistent findings, any specific onset of action claim for label is difficult to support.

Safety assessment

Safety of DCL 5mg dose in general is supported by the submitted data. Safety assessment of DCL is primarily based on the multi-dose efficacy and safety studies, and single-dose onset of action studies. Safety assessment included reporting of adverse events, vital signs, physical examination, clinical laboratory tests, and ECGs. Clinical laboratory tests and ECGs were done at baseline and at the last visit when the patients were still on the drug. ECGs were done at or near the T_{max}.

The maximum duration of exposure to DCL in the NDA database was 4 weeks that occurred in study C98-225. There is no long-term safety data in this application. Typically for a new molecular entity safety data from 300 patients exposed for 6 months and 100 patients for a 12 months is required. The Agency previously agreed that safety data from loratadine could be taken to support long-term safety of DCL, ~~provided the proposed clinical dose did not result in higher exposure to DCL and its metabolites than from the approved 10 mg dose of loratadine~~ ((Telecon minutes August 27, 1998; Telecon minutes September 30, 1998). Study P00117 (reviewed above) showed that exposure from DCL 5 mg dose was comparable to that from loratadine 10 mg dose.

The most common adverse event across all studies and treatment groups was headache (reported by 17-23% patients in multiple-dose studies and 3-5% in single-dose studies). Incidence of headache was not different among the treatment groups. Other frequently reported adverse events were somnolence, dysmenorrhea, and pharyngitis. Incidence of dysmenorrhea and pharyngitis was not different between the groups. Somnolence, fatigue, and dry mouth are adverse events commonly associated with antihistamines. Somnolence and fatigue reflects sedation, and dry mouth reflects anticholinergic effect. Incidence of these three adverse events is shown in Table 17. These adverse events had dose-ordering.

Physical examination and clinical laboratory tests did not show any clinically meaningful differences between the treatment groups.

Table 17. Selected adverse events for DCL 5 mg and placebo from multi-dose efficacy and safety st

	Placebo (n=661)	DCL 2.5 mg (n=173)	DCL 5 mg (n=659)	DCL 7.5 mg (n=662)	DCL 10 mg (n=172)	DCL 20 mg (n=172)
Somnolence	16 (2 %)	6 (2 %)	17 (3 %)	18 (3 %)	9 (5 %)	13 (8 %)
Fatigue	11 (2 %)	4 (2 %)	21 (3 %)	21 (3 %)	7 (4 %)	9 (5 %)
Dry mouth	12 (2 %)	7 (4 %)	24 (4 %)	14 (2 %)	4 (2 %)	7 (4 %)

Source: vol 140, p 29

Some second-generation antihistamines have been associated with QT prolongation and serious cardiac arrhythmia. Because of that, cardiac safety of DCL was specifically reviewed. Summary results of relevant ECG parameters from the dose-ranging study and three phase 3 studies are shown in Table 18. DCL caused a small dose-dependent increase in heart rate, possibly from anticholinergic effect. Uncorrected QT and Fredericia's corrected QTc did not change appreciably on DCL treatment. A small dose-dependent prolongation of QTc was seen on Bazett's correction. Since DCL caused increase in heart rate, Bazett's correction is possibly not appropriate for QT assessment for DCL.

Table 18. Change from baseline in ECG parameters from multiple-dose efficacy and safety studies

Parameters	Placebo	DCL 2.5 mg	DCL 5 mg	DCL 7.5 mg	DCL 10 mg	DCL 20 mg
Ventricular rate (bpm)	0.1	1.5	0.8	1.4	2.3	4.5
RR interval (msec)	0.4	2.1	1.2	0.2	3.3	-1.7
QT (uncorrected)	-0.4	-1.7	-3.2	-2.4	-2.6	-9.3
QTcF (Fridericia correction)	-0.2	-0.7	-1.5	0.1	1.5	-1.4
QTcB (Bazett's correction)	-0.1	2.0	-0.6	1.5	3.8	2.8

Source: vol 1, p 72; vol 150, p 6, March 20, 2000 submission

Cardiac safety of DCL was also assessed on two studies where DCL 7.5 mg was administered with ketoconazole or with erythromycin for 10 days, and in one study where DCL 45 mg (nine times the proposed dose) was administered for 10 days. A small PK interaction was seen with resulting increase in DCL exposure by about 24 % with ketoconazole and 14 % with erythromycin, based on AUC calculation. In the two drug interaction studies QTc interval was not appreciably prolonged. In the high dose cardiac safety study QTc interval was prolonged by 4 msec over placebo. The sponsor's analyses were based on machine read QTc intervals using only the maximum QTc values from the serial QTc readings. These limit the strength of the results. Given the negative preclinical cardiac findings with DCL (whole animal study, action potential duration study in guinea pig ventricular papillary muscles, and potassium channel studies), DCL is not expected to have a significant QT effect. The submitted analyses support this. However, for complete cardiac safety assessment and for labeling purposes, the sponsor should recalculate the QT data using correct methodologies at least for the high dose cardiac safety study C98-357. An appropriately trained clinician should read the ECG blinded to randomization schedule and assess the QT interval using a digitizing pad or other appropriate method, and look for morphological changes in T waves and U waves as well. A detail analyses on QTc data using the human read values should be performed. In addition to maximum QTc values, analyses should also be done with other QTc values, such as mean and AUC from serial ECGs.

Financial disclosure

Chances of biasing the NDA database are limited because all participated in double-blind, parallel-group, multi-center studies.

Data integrity

Data integrity in the clinical studies was verified by analyses of the electronic data set by biostatistics reviewer, and by DSI audit.

These sites were chosen based on their contribution to the clinical program. DSI investigators identified no major deficiencies that could compromise the data integrity.

Recommendation

From a clinical standpoint this NDA is recommend an APPROVABLE action.

Efficacy of DCL 5 mg for relief of symptoms of SAR, and general safety of DCL 5 mg is supported by the submitted data. However, the ECG data from cardiac safety studies (C98-352, C98-353, C98-357) are not adequately presented. The sponsor will need to reread the ECG, reanalyze, and resubmit the results. The proposed label statement that DCL is not supported by the submitted data. Based on sponsor's analysis, QTc was prolonged by 4 msec over placebo in that study.

Effect size of DCL 5 mg over placebo, and efficacy of DCL overall was not impressive. ~~The efficacy claims in general are overstated in the label and will need to be toned down to appropriately reflect the data. Specifically claims that DCL~~

will need to be removed from the label.

does not add anything more to the label over symptom benefit claims.

In various parts of the label, claims are made or implied for DCL. In apparent support of the claims, the clinical pharmacology section of the label includes results of studies claiming that DCL

Claims relating to action and related study results should be removed from the label.

Label claims that DCL metabolism is not changed in hepatic or renal dysfunction do not appear to be substantiated by the submitted data. The biopharmaceutics reviewer will need to comment on this and decide whether dose adjustment will be necessary or not for patients with liver and kidney dysfunction.

APPEARS THIS WAY
ON ORIGINAL

**Division of Pulmonary and Allergy Drug Products
CONSUMER SAFETY OFFICER REVIEW**

Application Number: NDA 21-165

Name of Drug: Clarinex® (desloratadine) Tablets

Sponsor: Schering Corporation

Material Reviewed:

**Submission Date(s): BL Dated December 14, 2001 (Package insert)
BL Dated December 18, 2001 (Carton and container labeling)**

Background

Labeling discussions with Schering took place over period of December 6, 2001, through December 10, 2001, with an additional discussion on December 13, 2001, to correct several typographic errors that were discovered in the BL dated December 10, 2001.

Summary

1. December 6, 2001 - Division sent a marked up copy of the working label with suggested changes, via facsimile. This facsimile also included a statement regarding immediate container labeling, "The 'Artwork 10 Tablet Blister' does not indicate the placement of the lot number (see submission dated November 10, 2000). Please submit an official copy that indicates the placement of the lot number."

2. December 6, 2001 - Schering replied with a facsimile accepting all suggested changes, "with the exception of the last sentence of the metabolism subsection of **CLINICAL PHARMACOLOGY**." Stating, '

The facsimile also included "ARTWORK 10 Table Blister" that included lot number, as requested.

3. December 7, 2001 - During a telephone conversation between Dr. Robert Meyer, Director, DPADP and Dr. Joseph Lamendola, Vice President, Regulatory Affairs, Schering Corporation, the following wording was agreed to regarding the last sentence of the metabolism section, "Although not seen in these pharacokinetic studies, patients who are slow metabolizers may be more susceptible to dose related adverse events." Schering confirmed this wording via facsimile transmission dated December 7, 2001.

In addition to the discussion the metabolism section, the Division suggested alternative wording to the last paragraph of the **Adverse Reactions** section, “;

* During this discussion the term hepatitis was not suggested as best reflecting what is actually being observed (several options were discussed). Dr. Meyer asked Schering to suggest one or two terms that more accurately reflect what is being observed.

4. December 7, 2001 – Schering responded to previous discussion with a fax suggesting the following wording, “The following spontaneous adverse events have been reported during the marketing of desloratadine: tachycardia, and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema, dyspnea and anaphylaxis),

During a subsequent teleconference, Schering was informed that qualifiers, such as, ‘
are not acceptable, Schering agreed to remove ‘

The phrase, ‘
’ was also discussed, it was suggested that this is still not the best phrase to describe what has been observed.

5. December 10, 2001 – In response to the ~~December 7, 2001~~, discussion, Schering sent in a facsimile with the following wording, “The following spontaneous adverse events have been reported during the marketing of desloratadine: tachycardia, and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema, dyspnea and anaphylaxis), and elevated liver enzymes including ,

Following receipt of this facsimile, a teleconference was held. Dr. Chowdhury suggested that
: be replaced with bilirubin. Mr. McHugh accepted this change (**See teleconference minutes for details**).

In response to the teleconference, Schering sent a facsimile labeled “Final Draft Label” incorporating all changes that were agreed to.

6. December 13, 2001 – Telephone conversation between Dan McHugh (Schering) and Anthony Zeccola (FDA) regarding four errors that were discover in the label by Schering:

1) First sentence under Hepatic Impairment should read: “hepatic impairment as defined by the Child-Pugh...” not

– This change was made by the Agency on 12/06/01.

2) In the Gender section, second sentence: 3-hydroxy desloratadine was corrected to 3-hydroxydesloratadine to be consistent with the document.

2) The third line in the title of Table 2 should read: “Trial in Patients With Seasonal Allergic Rhinitis” not

Correct text was in 12/6/01 fax from Agency.

3) Two corrections in the OVERDOSAGE section: The spelling of "Fridericia" was corrected. The fifth sentence should read "...mean increase of 8.1 msec in CLARINEX-treated subjects relative to placebo." not

This change was made by the Agency on 12/06/01.

4) In DOSAGE AND ADMINISTRATION, renalimpairment should read renal impairment.

Because these were items that had all ready been discussed by the Division and omitted from interim drafts, Schering was requested to incorporate them and send in new draft label.

7. December 17, 2001 – Receipt of electronic version submitted as Final Draft Label

8. December 18, 2001 – Schering submitted hardcopy of Final Draft Label, including full color renditions of the immediate container and carton labels.

Review

Electronic submission of the Final Draft Label received December 17, 2001. A visual line-by-line comparison found that this version contained all items agreed to as of December 13, 2001.

Conclusions

All appropriate changes have been implemented as discussed above.

/s/

Anthony M. Zeccola
Regulatory Management Officer

Supervisory Comment/Concurrence:

/s/

/s/

Sandra L. Barnes
Chief, Project Management Staff

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: December 10, 2001
TIME: 10:30 AM
LOCATION: Zeccola's Office
APPLICATION: NDA 21-165 - Clarinex

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Badrul Chowdhury, M.D.	Medical Officer	Pulmonary & Allergy Drug Products (DPADP) HFD-570
13. Anthony Zeccola	Regulatory Management Officer	DPADP

12/21/01

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Daniel McHugh	Regulatory Affairs	Schering Plough

Background: This was an impromptu teleconference to discuss two issues relating the labeling for NDA 2-165, Clarinex.

Discussion

1. On Page 3 of the current version of the label, in the Metabolism section, the statement, " is not entirely accurate since, reflects both adults and children. The Applicant proposed to change the sentence to read, "In pharmacokinetic studies (n=1087), approximately 7% of subjects were slow metabolizers of desloratadine..."
Dr. Chowdhury agreed that this is acceptable.
2. Earlier today the Division received a facsimile transmission from the Applicant with proposed wording for the Adverse Events section, with regard to elevated liver enzymes. (This facsimile was in response to discussions between the Division and Applicant which took place on Friday

Page 2

December 7, 2001). In this facsimile, the Applicant proposed the following wording, "The following spontaneous adverse events have been reported during the marketing of desloratadine: tachycardia and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema. Dyspnea and anaphylaxis) and elevated liver enzymes including

Following review of the proposal, the Division suggested the following wording instead, "The following spontaneous adverse events have been reported during the marketing of desloratadine: tachycardia and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema. Dyspnea and anaphylaxis) and elevated liver enzymes including bilirubin."

Mr. McHugh agreed to the wording of the sentence as suggested by the Division.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: December 7, 2001
To: Daniel McHugh
Fax No.: 908-740-4131
From: Anthony M. Zeccola
Regulatory Management Officer
Through: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
Subject: Clarinex Label

Number of Pages: 2 (Including this page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission. I may be reached on 301-827-1058.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

/s/

12/21/01

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products

This facsimile transmission includes the most recent changes that were discussed during the December 7, 2001 teleconference between the Division of Pulmonary and Allergy Drug Products and Schering Corporation. During this discussion, Dr. Robert Meyer* suggested alternate wording to the **Adverse Reactions** section of the label based on review of the December 5, 2001 Safety Update. Dr. Joseph Lamendola, representing Schering Corporation, agreed to take these suggestions under consideration and requested the proposal in writing via facsimile transmission.

The following is the proposed wording that was discussed during the teleconference:

“..... gender, age, or race.

.....
DRUG ABUSE AND ...”

*** Teleconference Participants.**

Representing Schering Corporation:

Joseph Lamendola, Ph.D., Vice President, U.S. Regulatory Affairs

Representing FDA:

Robert J. Meyer, M.D., Director, Division of Pulmonary and Allergy Drug Products

Badrul Chowdhury, M.D., Medical Team Leader

Anthony M. Zeccola, Regulatory Management Officer

Memorandum of Telephone Facsimile Correspondence

Date: December 6, 2001
To: Mary Jane Boyle
Fax No.: 908-740-4131
From: Anthony M. Zeccola
Regulatory Management Officer
Through: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
Subject: Clarinex Label

Number of Pages: 17 (Including this page)

We are providing the attached information via telephone facsimile ~~for your convenience, to expedite the progress of your drug development program.~~ This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission. I may be reached on 301-827-1058.

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Thank you.

IS/ 12/21/01

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products

This facsimile transmission includes the most recent changes that are suggested following review by the Division of Pulmonary and Allergy Drug Products and the Office of Drug Evaluation II. Please incorporate these changes and submit an official copy which includes these changes.

Note: In the Metabolism section, please fill in the numbers in the following statement, "... (approximately xx% of blacks were slow metabolizers in pharmacokinetic studies, n=xxx)."

Also note that the post-marketing subsection of the labeling has not been finally reviewed against the safety update data. We may have further comments for this subsection following this review.

Additional Comment:

The "Artwork 10 Tablet Blister" does not indicate the placement of the lot number (see submission dated November 10, 2000). Please submit an official copy that indicates the placement of the lot number.

APPEARS THIS WAY
ON ORIGINAL

PROJECT MANAGER LABELING REVIEW

NDA: 21-165
APPLICANT: Schering
SUBMISSION: BL dated February 13, 2001
PROJECT MANAGER: Gretchen Trout

BACKGROUND: On January 19, 2001, the Division issued an approvable letter that included labeling comments. This submission is in response to the approvable letter.

REVIEW: The applicant made all of the revisions requested in the January 19, 2001 letter. In addition to the requested changes, they proposed revisions to the OVERDOSAGE section with regard to changes in QTc and heart rate. The clinical and biometrics reviewers will need to comment on these changes.

Gretchen Trout

See electronic signature

5/15/01
/S/

Project Manager
Division of Pulmonary and Allergy Drug Products

INDUSTRY TELECONFERENCE MINUTES

DATE: January 10, 2001

NDA: 21-165

PRODUCT: Clarinex (desloratadine) Tablets

SPONSOR: Schering

FDA PARTICIPANTS:

Robert Meyer, Division Director

Gretchen Trout, Project Manager

SPONSOR PARTICIPANTS:

MaryJane Boyle

Alex Giaquinto

Joe Lamendola

Peter Martin

BACKGROUND: The Division sent labeling comments to Schering via facsimile on January 8, 2001. Schering requested this teleconference to discuss the Agency's comments.

Dr. Meyer notified Schering that many of the labeling revisions originated from the Office level. This telecon meeting is being conducted to allow Schering to state any concerns with the revisions to the package insert. However, since we will have to take Schering's concerns back to the Office before we can give a final decision, this telecon is not intended to arrive at final agreements.

The discussion on the package insert proceeded in order.

Clinical Pharmacology:

1 pages redacted from this section of
the approval package consisted of draft labeling

CONCLUSION: Schering will fax a revised package insert which the Division will discuss with the Office.

Schering also notified the Division that they are withdrawing the Kenilworth site from the NDA at this time.

JANUARY 11, 2001

Gretchen Trout and Dan McHugh

Schering sent a revised package insert via facsimile on January 10, 2001. Ms Trout telephoned Mr. McHugh and requested that Schering include additional information under the Total Symptom Score (TSS) table in the Clinical Trials section. Specifically Schering should state what the range of TSS is; e.g., 0 = no symptoms, and 24 = maximal symptoms. Schering should also explain that a decrease in symptom score indicates a decrease in symptoms. Ms. Trout informed Mr. McHugh that there may be additional comments after we have discussed the package insert with the Office.

JANUARY 11, 2001

Schering submitted a revised package insert with additional information included with the TSS table.

JANUARY 16, 2001

FDA: Bob Meyer, Gretchen Trout
Schering: Alex Giaquinto, Joe Lamendola

In two teleconferences on this day comments were conveyed from the Division to Schering on the package insert. As a result of these teleconferences, Schering submitted a revised package insert on January 18, 2001, which addressed all of the Agency's comments.

Dr. Meyer also explained that the Agency would not take an action on this application until we have an overall recommendation from our Office of Compliance. This recommendation will be based on site specific and product specific investigations, as well as general GMP issues.

**APPEARS THIS WAY
ON ORIGINAL**



Memorandum of Facsimile Correspondence

Date: January 8, 2001

To: Mary Jane Boyle

FAX: 908-740-4131

From: Gretchen Trout

Subject: Labeling comments

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Thank you.

16 pages redacted from this section of
the approval package consisted of draft labeling

T3cul

Memorandum of Telephone Facsimile Correspondence

Date: October 27, 2000
To: Mary Jane Boyle
Fax: (908) 740-6500
From: Vicky Borders-Hemphill
Project Manager
Subject: NDA 21-165
October 27, 2000 teleconference

Reference is made to the meeting/teleconference held between representatives of your company and this Division on October 27, 2000. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-5580.

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Thank you.

INDUSTRY TELECONFERENCE MINUTES

DATE: October 27, 2000

NDA: 21-165

PRODUCT: desloratadine

SPONSOR: Schering

FDA PARTICIPANT:

Vicky Borders, Project Manager

SPONSOR PARTICIPANT:

Mary Jane Boyle, Regulatory Affairs

BACKGROUND: Reference is made to Schering's facsimile dated October 25, 2000, of revised labeling and also to revisions discussed in the October 24, 2000, teleconference between Drs. Meyer and Giaquinto. FDA contacted Schering to convey changes.

SUMMARY:

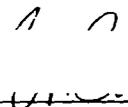
~~FDA directed Schering to the Clinical Pharmacology section, Mechanism of Action subsection of the labeling and requested that the following sentence be deleted from the labeling.~~

FDA directed Schering to the Pharmacodynamics section, Effects of QTc subsection of the labeling and requested that the following 2 sentences be deleted:

The 2 sentences are to be replaced with the following 2 sentences:

FDA explained that the use of the word " " in place of " " in the sentence, " " is acceptable.

Schering agreed to make the changes and resubmit draft labeling no later than Monday, October 30, 2000.



Vicky Borders
Project Manager

Trout

Record of Telephone Conversation

Date: August 22, 2000
Subject: [] and NDA 21-165
Initiated by: Applicant
Product Name: [] and desloratadine (5 mg) tablets
Firm Name: Schering Corporation
Contact: Dr. Alex Giaquinto; Dr. Diane Zezza
Telephone Number: 908-740-5770

First call: I was called by Dr. Giaquinto, who was looking to speak with Dr. Poochikian. I said that Dr. Poochikian was away this week. He indicated that they had [] and they wished to have a meeting or a teleconference for clarification. They would like to avoid multiple cycles. I said that I thought that Dr. Poochikian should be involved in such a meeting. Dr. Giaquinto would like to meet with us next week. He didn't know who is the reviewer for this product. I indicated that for simple clarification it might be possible to have a teleconference next week but that the primary reviewer needs to be here.

Dr. Giaquinto also indicated that they are expecting a letter for desloratadine (5 mg) tablets (NDA 21-165), and they would like to discuss this also at the same meeting. I said I would check into these issues.

Second call: I called Dr. Giaquinto's office, and I found that he was not available but that he had asked Dr. Zezza to speak with me. I told her of Dr. Giaquinto's earlier conversation with me, and I indicated that Dr. Craig Bertha is the primary reviewer [] Dr. Bertha is away this week. Since various people involved are on leave or will be on leave at this time of year, it would be best for her to contact the project manager for [] Mr. David Hilfiker. Mr. Hilfiker can check schedules and set up the meeting. They should indicate in writing the purpose of the meeting and the specific issues that they would like to have clarified.

I indicated that a letter for desloratadine (5 mg) tablets (NDA 21-165) would be issued shortly. She asked if that meant this week. I said that I couldn't guarantee that, but that the letter was in process and would probably be sent this week or next week. I said that we can't discuss a letter (for desloratadine) that they haven't received yet, and that they can see if they need any clarification when they receive it. She agreed to this and thanked me.


 Alan C. Schroeder, Ph.D.

cc: [] Dup. NDA 21-165 HFD-570/Division file HFD-570/ACSchroeder/8-22-2000 HFD-570/GPoochikian HFD-570/CSO DHilfiker HFD-570/KSwiss HFD-570/GTrout	HFD-570/CBertha R/D init. by: ACS for Gp 8/22/00 F/T by: ACSchroeder/8-22-2000 ACSfile: []
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INDUSTRY TELECONFERENCE MINUTES

DATE: July 18, 2000

NDA 21-165

PRODUCT: desloratadine

SPONSOR: Schering

FDA PARTICIPANTS:

Tim McGovern, Pharmacology Reviewer

Joe Sun, Pharmacology Team Leader

Gretchen Trout, Project Manager

SPONSOR PARTICIPANTS:

Alex Giaquinto, Regulatory Affairs

Satish Joshi, Regulatory Affairs

Joe Lamendola, Regulatory Affairs

Elmer Mirro, Pre-Clinical Drug Safety

Nick Pellicione, Regulatory Affairs

BACKGROUND: Schering requested this teleconference to discuss comment 13 from the Division's June 26, 2000, letter pertaining to toxicology qualification studies for impurities and Reference is made to the meeting request dated July 13, 2000.

Schering wanted to discuss what is necessary to qualify the impurities. In the Division's letter we requested a 3-month study in one species, Schering had submitted two 1-month studies in two species. Schering stated that, based upon their understanding, one-month studies are sufficient. The Division replied that impurity qualification for drugs used chronically or chronic-intermittently we require three-months in one species. Schering asked what guidance they can refer to because in the ICH guidance there is no connection of the duration of the study with the use of the compound. The Division replied that the ICH guidance states that studies up to 90 days may be required.

Schering referenced their existing toxicology studies in rats and monkeys that were conducted up to three-months where, even though the impurity levels were not up to reached levels and with the doses used were very high: in one rat study they have a 480 dose multiple, and a 96 dose multiple for monkey. Schering believes that this gives them tremendous assurance that they have evaluated the safety of these impurities. The Division replied that if the levels referenced by Schering were reached and the animals have

been exposed to the stated levels for at least 3 months in duration, the studies would be adequate to qualify the impurities. Schering should submit these data directly to Dr. McGovern and include specifics on the study and the batch analysis.


Gretchen Trout
Project Manager

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/28/00

DUE DATE: 6/15/00

OPDRA CONSULT #: 00-0100

TO:

Robert Meyer, M.D.
Director, Division of Pulmonary & Allergy Drug Products
HFD-570

THROUGH:

Gretchen Trout
Project Manager
HFD-570

PRODUCT NAME:

Clarinet
(desloratadine tablets) 5 mg

IND#:

MANUFACTURER: Schering Corporation

SAFETY EVALUATOR: P. Tam, RPh.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Clarinet. We do not recommended use of the name See the checked box below.

✓ **FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

JS/ *6/2/2000*

JS/ *6/5/00*

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration