

TABLE (continued)

Mean change from baseline over 2 weeks (p value vs placebo)(ITT)

Parameter	Time measured	2.5 mg DCL	5 mg DCL	7.5 mg DCL	10 mg DCL	20 mg DCL
Nasal congestion	AM/PM reflective (t19, p62, v1.120)	-0.4 (0.86) ** placebo -0.4	-0.5 (0.04)	-0.5 (0.04)	-0.5 (0.19) **	-0.6 (< 0.01)
Nasal congestion	AM/PM point in time	-0.3 (0.88) ** placebo -0.3	-0.5 (0.05)	-0.5 (0.03)	-0.5 (0.06) **	-0.6 (< 0.01)
Nasal congestion	AM reflective (t2b, p594, v1.121)	-0.3 (0.59) ** placebo -0.4	-0.5 (0.10) **	-0.5 (0.12) **	-0.4 (0.51) **	-0.6 (< 0.01)
Nasal congestion	AM point in time	-0.3 (0.51) ** placebo -0.3	-0.4 (0.19) **	-0.5 (0.13) **	-0.5 (0.10) **	-0.5 (< 0.01)
Nasal congestion	PM reflective	-0.4 (0.72) ** placebo -0.4	-0.5 (0.03)	-0.6 (0.01)	-0.5 (0.06) **	-0.7 (< 0.01)
Nasal congestion	PM point in time	-0.4 (0.73) ** placebo -0.3	-0.5 (0.02)	-0.5 (0.02)	-0.5 (0.06) **	-0.6 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Rhinorrhea	AM/PM reflective	-0.3 (0.90) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.5 (0.11) **	-0.6 (< 0.01)
Rhinorrhea	AM/PM point in time	-0.4 (0.45) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.5 (0.03)	-0.6 (< 0.01)
Rhinorrhea	AM reflective (t1b, p592, v1.121)	-0.3 (0.58) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (0.06) **	-0.4 (0.30) **	-0.5 (0.01)
Rhinorrhea	AM point in time	-0.3 (0.54) ** placebo -0.3	-0.5 (0.02)	-0.5 (0.01)	-0.4 (0.04)	-0.5 (< 0.01)
Rhinorrhea	PM reflective	-0.4 (0.79) ** placebo -0.4	-0.6 (0.01)	-0.6 (< 0.01)	-0.5 (0.06) **	-0.6 (< 0.01)
Rhinorrhea	PM point in time	-0.4 (0.41) ** placebo -0.3	-0.5 (0.02)	-0.6 (< 0.01)	-0.5 (0.05)	-0.6 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Nasal itching	AM/PM reflective	-0.4 (0.06) ** placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
Nasal itching	AM/PM point in time	-0.5 (0.06) ** placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
Nasal itching	AM reflective (t3b, p596, v1.121)	-0.4 (0.09) ** placebo -0.3	-0.6 (< 0.01)	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.6 (< 0.01)
Nasal itching	AM point in time	-0.4 (0.16) ** placebo -0.3	-0.5 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)
Nasal itching	PM reflective	-0.5 (0.05) placebo -0.4	-0.6 (< 0.01)	-0.7 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
Nasal itching	PM point in time	-0.5 (0.03) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Sneezing	AM/PM reflective	-0.5 (0.12) ** placebo -0.4	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (0.01)	-0.7 (< 0.01)
Sneezing	AM/PM point in time	-0.5 (< 0.01) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
Sneezing	AM reflective (t4b, p598, v1.121)	-0.4 (0.27) ** placebo -0.3	-0.5 (< 0.01)	-0.6 (< 0.01)	-0.5 (0.04)	-0.6 (< 0.01)
Sneezing	PM reflective	-0.6 (0.07) ** placebo -0.4	-0.7 (< 0.01)	-0.7 (< 0.01)	-0.7 (< 0.01)	-0.8 (< 0.01)
Sneezing	AM point in time	-0.5 (0.05) placebo -0.3	-0.5 (0.01)	-0.6 (< 0.01)	-0.5 (0.02)	-0.7 (< 0.01)
Sneezing	PM point in time	-0.6 (< 0.01) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.8 (< 0.01)

Change from baseline over 2 weeks (p value vs placebo)(ITT)

Parameter	Time measured	2.5 mg DCL	5 mg DCL	7.5 mg DCL	10 mg DCL	20 mg DCL
Itching eyes	AM/PM reflective (t20, p64, v1.120)	-0.5 (0.03) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.5 (< 0.01)	-0.7 (< 0.01)
Itching eyes	AM/PM point in time	-0.5 (< 0.01) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)
Itching eyes	AM reflective (t5b, p600, v1.121)	-0.4 (0.05) placebo -0.3	-0.6 (< 0.01)	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.7 (< 0.01)
Itching eyes	AM point in time	-0.5 (0.01) placebo -0.3	-0.5 (0.02)	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.6 (< 0.01)
Itching eyes	PM reflective	-0.5 (0.07) ** placebo -0.4	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
Itching eyes	PM point in time	-0.6 (< 0.01) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.7 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Tearing eyes	AM/PM reflective	-0.4 (0.23) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (0.02)	-0.5 (0.02)	-0.6 (< 0.01)
Tearing eyes	AM/PM point in time	-0.5 (0.04) placebo -0.3	-0.5 (0.06) **	-0.5 (< 0.01)	-0.5 (0.02)	-0.5 (< 0.01)
Tearing eyes	AM reflective (t6b, p602, v1.121)	-0.3 (0.27) ** placebo -0.3	-0.5 (< 0.01)	-0.4 (0.03)	-0.4 (0.02)	-0.6 (< 0.01)
Tearing eyes	AM point in time	-0.4 (0.07) ** placebo -0.3	-0.4 (0.08) **	-0.4 (< 0.01)	-0.5 (0.04)	-0.5 (< 0.01)
Tearing eyes	PM reflective	-0.5 (0.27) ** placebo -0.4	-0.5 (0.19) **	-0.5 (0.08) **	-0.5 (0.12) **	-0.6 (< 0.01)
Tearing eyes	PM point in time	-0.5 (0.04) placebo -0.3	-0.5 (0.08) **	-0.6 (< 0.01)	-0.5 (0.02)	-0.6 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Redness eyes	AM/PM reflective	-0.3 (0.47) ** placebo -0.3	-0.5 (0.01)	-0.5 (< 0.01)	-0.4 (0.13) **	-0.5 (< 0.01)
Redness eyes	AM/PM point in time	-0.4 (0.29) ** placebo -0.3	-0.4 (0.08) **	-0.5 (< 0.01)	-0.4 (0.15) **	-0.5 (0.02)
Redness eyes	AM reflective (t7b, p604, v1.121)	-0.3 (0.88) ** placebo -0.3	-0.4 (0.03)	-0.4 (0.02)	-0.4 (0.19) **	-0.5 (< 0.01)
Redness of eyes	AM point in time	-0.3 (0.41) ** placebo -0.3	-0.4 (0.26) **	-0.5 (0.01)	-0.4 (0.20) **	-0.4 (0.04)
Redness eyes	PM reflective	-0.4 (0.24) ** placebo -0.3	-0.5 (0.03)	-0.6 (< 0.01)	-0.4 (0.18) **	-0.5 (< 0.010)
Redness eyes	PM point in time	-0.4 (0.24) ** placebo -0.3	-0.5 (0.04)	-0.6 (< 0.01)	-0.4 (0.17) **	-0.5 (0.02)
*****	*****	*****	*****	*****	*****	*****
Itching ears, palate	AM/PM reflective	-0.4 (0.09) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.5 (0.01)	-0.5 (< 0.01)
Itching ears, palate	AM/PM point in time	-0.4 (0.01) placebo -0.2	-0.5 (< 0.01)	-0.6 (< 0.01)	-0.5 (< 0.01)	-0.6 (< 0.01)
Itching ears, palate	AM reflective (t8b, p606, v1.121)	-0.4 (0.17) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.4 (0.02)	-0.5 (< 0.01)
Itching ears, palate	AM point in time	-0.4 (0.03) placebo -0.2	-0.5 (< 0.01)	-0.6 (< 0.01)	-0.5 (< 0.01)	-0.5 (< 0.01)
Itching ears, palate	PM reflective	-0.4 (0.09) ** placebo -0.3	-0.5 (< 0.01)	-0.5 (< 0.01)	-0.5 (0.01)	-0.5 (< 0.01)
Itching ears, palate	PM point in time	-0.5 (< 0.01) placebo -0.3	-0.6 (< 0.01)	-0.6 (< 0.01)	-0.5 (0.01)	-0.6 (< 0.01)
*****	*****	*****	*****	*****	*****	*****
Global evaluation	Tab 21, pgs 67-68, v 1.120	0.21 **	0.13 **	< 0.01	0.14	0.08
Therapeutic response	Tab 22, p70, v 1.120	0.23 **	0.05	< 0.01	0.03	< 0.01

** no statistically significant difference from placebo

➤ safety:

➤ Adverse Events: The overall incidence of AEs was 43%, 40%, 38%, 44%, 47% and 37% of the 2.5 mg, 5 mg, 7.5 mg, 10 mg, 20 mg, and placebo groups, respectively. In terms of AEs with an incidence of 1% or greater in any treatment group, there was an incidence of 2% or greater than the incidence seen in the placebo group for at least one of the DCL treatment groups for dry mouth (4% in the 2.5 and 20 mg DCL groups and 2% in the placebo group), fatigue (3% in the 5 and 7.5 mg DCL groups, 4% in the 10 mg DCL group, 5% in the 20 mg DCL group and 1% in the placebo group), fever (2% in the 20 mg DCL group and none in the placebo group), headache (21%, 16%, 18%, 17%, 21% and 14% in the 2.5 mg, 5 mg, 7.5 mg, 10 mg, 20 mg and placebo groups, respectively), myalgia (3% in the 2.5 mg DCL group and 2% in the 10 mg and 20 mg DCL groups, compared to none in the placebo group), and somnolence (4% in the 7.5 mg DCL group, 5% in the 10 mg DCL group, 8% in the 20 mg DCL group and 2% in the placebo group). In terms of AEs considered to be related to the administration of DCL, headache, fatigue and somnolence were associated with a 2% or greater incidence than seen with placebo and were more likely to occur with this greater incidence at higher doses and to be more severe. There were 2 patients who received 5 mg of DCL who discontinued treatment because of dry mouth and fatigue. Among the patients who received 10 mg DCL, there was one patient who discontinued because of fatigue and irritability, one because of fatigue and somnolence and one because of somnolence and impaired concentration. There was one patient who received 20 mg of DCL who discontinued because of drowsiness and one placebo patient who discontinued because of somnolence. One patient receiving 7.5 mg of DCL temporarily interrupted treatment due to severe fatigue.

Comment: Dry mouth is an expected side effect of antihistamines. Somnolence and fatigue have not been associated with non-sedating antihistamines at the recommended doses. There is a dose-response in terms of fatigue beginning at 5 mg DCL and somnolence beginning at 7.5 mg DCL that is compatible with a sedative effect. These side effects were of sufficient severity to cause patient discontinuation at a dose of 5 mg DCL. The incidence of sedation was, however, very low in all groups that received DCL.

- **laboratory values:** The majority of laboratory values outside the normal reference range were seen at screening. Values outside the normal reference were seen with the same or greater frequency after administration of placebo as after administration of DCL. There was no significantly greater number of patients with abnormal lab values, such as low WBC count, increased LFTs, increased blood glucose or 3+ urinary protein, in any of the DCL groups than in the placebo group or than was seen at baseline. In addition, there was no significantly greater frequency of any abnormal laboratory value with higher doses of DCL than with lower doses. There were 19 patients in the 20 mg DCL group whose blood glucose increased from a normal level to above normal compared to 10 patients in the placebo group. However, more patients in the 2.5 mg DCL group (15) had an increase in blood glucose from low or normal to high than in the 7.5 mg DCL group (7) or the 10 mg DCL group (9). ~~In a similar fashion, there were 11 patient in the 7.5 mg DCL group who had an increase in SGPT from normal to high compared to 4 patients in the placebo group. However, there were 8 patients in the 5 mg DCL group and 6 patients in the 10 and 20 mg DCL groups who had such an increase. A similar pattern was seen for SGOT with more patients in the 5 mg DCL group having normal baseline levels and increased levels after treatment than in the placebo group, with the 10 and 20 mg DCL groups having an incidence comparable to placebo.~~
- **ECGs:** There was a mean decrease in both QT and QTc after administration of all doses of DCL and a slight prolongation after administration of placebo, using the Fridericia formula. The percentage of patients with a 10% or greater prolongation of the QT and QTc interval was equal or less than the placebo group in all groups treated with DCL, using the Fridericia formula.
- **Vital Signs:** There were significantly more patients in the 20 mg DCL group (12)(7%) that had a heart rate of 90 bpm or greater after treatment than in the placebo group (4)(2%), but only 2% and 4% of the 5 mg DCL and 7.5 mg DCL groups, respectively, had a heart rate of 90 bpm or greater after 2 weeks of treatment. Two patients in the 5 mg DCL group and 3 patients in the 7.5 DCL group had a 40% or greater increase in diastolic blood pressure, compared to none in the placebo

group. In the 20 mg DCL group, 5 patients had this degree of increase compared to only 1 patient in the 10 mg DCL group. One patient in the 7.5 mg DCL group, and two patients in the 20 mg DCL group compared with none in the 5 mg DCL and placebo groups had a 40% or greater increase from baseline in systolic blood pressure after two weeks. An increase in heart rate of 40% or greater was seen in 5 patients in the 20 mg DCL group compared to 3 in the placebo group after 2 weeks of treatment. An increase heart rate of 30-39% was seen in 7 patients in the 20 mg DCL group compared to 3 in the placebo group after 2 weeks of treatment. An increase in heart rate of 20-29% was seen in 10-14 patients who received DCL compared to 5 patients who received placebo after 2 weeks of treatment.

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ONSET OF ACTION STUDIES

Study 226: Outdoor (in the park) Onset of Action Study

Number of patients: 310 (155 in each treatment group)

Age range: 12-64 years

Patient population: SAR

Study design: 2 center, placebo-controlled, double-blind, single dose, randomized, parallel outdoor pollen-exposure study

Drug administration: DCL 5 mg

Periods of study: one week between screening and baseline visits; the baseline visit was one day prior to drug administration; evaluation over 5 hours on the study day

Parameters evaluated: the primary efficacy variable was onset of action, defined as the first time point that DCL produced an improvement that was statistically more than placebo, in terms of change from baseline in mean total symptom score (TSS) (nasal symptoms [rhinorrhea, nasal congestion, nasal itching and sneezing] and non-nasal symptoms [itching eyes, tearing eyes, itching ears and palate and cough]) and that continued to be statistically significantly different from placebo; each symptom scoring was based on point-in-time evaluation every 15 minutes for the first 2 hours and every 30 minutes for the following 3 hours using a 0-3 categorical scale; in addition, the patient was asked to render a reflective judgement on the response to treatment relative to baseline at each time point, using a categorical scale of 1-5.

Study results:

Efficacy: Because there was no statistically significant difference between DCL and placebo in terms of change from baseline in TSS ($p = 0.64$), time of onset could not be determined in this study. There was still no statistically significant difference between DCL and placebo if scores for nasal congestion and cough were excluded. The reason for failure to show a statistically significant difference between DCL and placebo appeared to be due to the significant placebo response, the reason for which is unclear. The maximum decrease in mean total symptom score was 10 in the DCL group and 9 in the placebo group after 5 hours when cough was included and 9 and 8 after 5 hours in the DCL and placebo groups, respectively, when cough was excluded. No statistically significant difference between DCL and placebo was seen for total nasal symptoms ($p = 0.32$), total non-nasal symptoms ($p = 0.92$) or any individual symptom (except for sneezing [$p = 0.03$]). There was no statistically significant difference for rhinorrhea ($p = 0.47$), nasal congestion ($p = 0.41$), nasal itching ($p = 0.65$), eye itching ($p = 0.54$), eye tearing ($p = 0.95$), itching ears/ palate ($p = 0.58$) or cough ($p = 0.10$). Nor was there any statistically significant difference between DCL and placebo in terms of patient assessment of response to treatment.

Safety: Headache was seen slightly more frequently in the DCL group (5%) than in the placebo group (3%), but there were no AEs that were considered severe.

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Study 367: Onset of Action Study in Environmental Exposure Unit

Number of patients: 360 (120 in each treatment group)

Age range: 16-65 years

Patient population: SAR

Study design: single dose, randomized, placebo-controlled, parallel, EEU, single center, double-blind study

Drug administration: DCL 5 mg and 7.5 mg

Periods of study: There were 3 periods of study: a screening period, a priming period (up to six 3 hour priming sessions within 14 days of treatment

Parameters evaluated: The primary efficacy variable was onset of action, defined as the first time point that DCL showed a statistically significant difference from placebo in terms of change from baseline in mean total symptom score (a combination of nasal symptoms [rhinorrhea, nasal congestion, nasal itching and sneezing] and non-nasal symptoms [itching of eyes, tearing of eyes, itching of ears/palate and cough]) that continued to be statistically significantly different from placebo. Evaluations were made every 15 minutes over the first two hours and every 30 minutes for the next 3 hours (total period of evaluation was 5 hours) and represented point-in-time and reflective assessment by patients of symptoms using a 0-3 categorical scale; evaluations were done excluding nasal congestion and cough; evaluation was done for nasal symptoms, non-nasal symptoms and individual symptoms; in addition, evaluation of therapeutic response was also evaluated by patients using a 1-5 categorical scale.

Study Results:

Efficacy: Onset of action was 2 hours after administration of 5 mg of DCL ($p = 0.04$) and 3.5 hours after administration of 7.5 mg of DCL ($p = 0.05$), based on TSS excluding cough. Mean percent reductions in total symptom score (excluding cough) was 53% (mean decrease in TSS of 9.1), 50% (mean decrease in TSS of 8.4) and 35% (mean decrease in TSS of 6.1) in the 5 mg DCL, 7.5 mg DCL and placebo groups, respectively. There was a statistically significant difference between the 5 mg DCL group and the placebo group in terms of total nasal symptom score 2 hours after drug administration ($p = 0.05$) and between the 7.5 mg DCL group and the placebo group 2.5 hours after drug administration ($p = 0.04$). There was a statistically significant difference between the 5 mg DCL group and the placebo group in terms of total non-nasal symptom score 1.75 hours after drug administration ($p = 0.04$) and between the 7.5 mg DCL group and the placebo group 4.5 hours after drug administration ($p = 0.02$). There was a great deal of variation in the onset of effectiveness of DCL in regard to individual symptoms. For example, statistically significant improvement for itching of the ears/palate occurred 1.5 hours after administration of 5 mg of DCL but not until 4.5 hours after administration of 7.5 mg of DCL. On the other hand, statistically significant improvement in rhinorrhea and nasal itching occurred 2 and 2.5 hours, respectively after administration of both doses of DCL. Statistically significant improvement in sneezing was not seen until 3 and 5 hours after administration of 5 and 7.5 mg of DCL, respectively, and was not seen for itching of the eyes until 3.5 and 5 hours after administration of 5 and 7.5 mg of DCL, respectively. Based on patient evaluation of therapeutic response, onset of action was 2 hours after administration of 5 mg of DCL and 2.5 hours after 7.5 mg DCL.

Safety: There was no greater incidence of specific AEs in the groups that received DCL than in the group that received placebo. There was only one severe treatment-related AE of headache in a patient who received 5 mg of DCL.

Study 448: Onset of Action Study (Vienna Challenge Chamber)

- **Number of patients: 60 randomized; 53 completed study; 7 discontinued**
 - **Age range: 19-41 years**
 - **Patient population: SAR exposed to 1500 grass pollen grains per cubic meter over 2 hours; baseline severity of symptoms was evaluated for 2 hours prior to drug administration**
 - **Study design: PC, SD, DB, R, CX, SC study**
 - **Drug administration: 5 mg and 7.5 mg of DCL**
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- **Periods of study: washout period of at least 10 days between the three treatment days; symptom evaluation was done every 15 minutes for the first 2 hours and every 30 minutes for the next 3 hours;**
- **Parameters evaluated: Onset of action was defined as the first time point that DCL showed a statistically significantly greater improvement than placebo in terms of change from baseline in TSS (8 symptoms, 4 nasal and 4 non-nasal) that remained statistically significantly better than placebo from that time point until the end of the study; total nasal and total non-nasal (including and excluding cough) and individual symptoms were also assessed by patients; patients did a point-in-time and reflective assessment (evaluation of therapeutic response based on a 1-5 categorical scale) of their symptoms at each time point; nasal symptoms included nasal congestion, rhinorrhea, nasal itching and sneezing while non-nasal symptoms included itching eyes, tearing eyes, itching ears/palate and cough; these symptoms were graded using a 0-3 categorical scale; safety parameters included VS and AEs.**

➤ Study Results:

* Efficacy: There was randomization of 60 patients. Of these, 59 received 5 mg of DCL and 56 received 7.5 mg of DCL and placebo. There were 53 patients in the ITT analysis and 52 patients in the efficacy evaluable subset of patients. Onset of effect was seen 1.25 hours after administration of 5 mg DCL (decrease of 6.0 compared to 4.8 for placebo) and 3.5 hours after administration of 7.5 mg DCL (decrease of 7.2 compared to 5.0 for placebo) whether cough was included or not. Mean percent reduction in TSS excluding cough was 48%, 45% and 26% in the 5 mg DCL, 7.5 mg DCL and placebo groups, respectively. The onset of effect was 1.5 hours in terms of nasal symptoms in the group that received 5 mg DCL (decrease of 3.1 compared to 2.2 for placebo) and 3.5 hours in the 7.5 mg DCL group (decrease of 3.7 compared to 2.3 for the placebo group). ~~Excluding cough, the onset of effect in terms of non-nasal symptoms was 1.75 hours in the 5 mg DCL group and 4 hours in the 7.5 mg group.~~ There was tremendous variation in the onset of effect for individual symptoms as indicated in the table below. In terms of patient evaluated therapeutic response (reflective assessment), onset of effect was seen after 1.25 hours in the group that received 5 mg DCL and 3.5 hours in the group that received 7.5 mg DCL.

Symptom	5 mg DCL	7.5 mg DCL
nasal congestion	4 hours	None
Rhinorrhea	4.5 hours	3.5 hours
Itching nose	1.75 hours	3.5 hours
Sneezing	1.5 hours	2 hours
Tearing eyes	5 hours	None
Itching eyes	1.75 hours	3.5 hours
Itching ears/palate	3.5 hours	4.5 hours
Cough	None	2.5 hours

Safety: No AEs were reported. No significant changes in VS was noted.

Comment: In both EEU studies, onset of action was seen significantly sooner in the group that received 5 mg than in the group that received 7.5 mg of DCL. The clinical significance, if any, of this finding is unclear.

Study 287: Onset of action study in EEU (Vienna Challenge Chamber)

- **Number of patients: 53 randomized; 52 completed the study**
 - **Age range: 19-42 years**
 - **Patient population: SAR**
 - **Study design: single dose, double-blind, randomized, placebo-controlled, crossover, single center study**
 - **Drug administration: 5 mg DCL**
 - **Periods of study: washout of 10 days between treatments; two study days when patients received DCL and placebo**
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- **Parameters evaluated: onset of action was defined as the first time point that there was a statistically significant difference between DCL and placebo in terms of change from baseline in TSS. TSS consisted of nasal congestion, rhinorrhea, itching of the nose, sneezing, itching of the eyes, tearing of the eyes and itching of the ears/palate; a statistically significant difference had to be maintained at subsequent time points; patient evaluation of symptoms was done every 15 minutes of the first 2 hours and every 30 minutes for the following 3 hours; patients were exposed to 1500 grass pollen grains per cubic meter of air for 2 hours prior to drug administration; evaluation by patients in terms of symptoms at a point-in-time and reflective (response to therapy), using a 0-3 categorical scale for symptom assessment and a 1-5 categorical scale for response to therapy**

Study Results:

Efficacy: A statistically significant improvement compared to placebo was seen 1.75 hours after administration of 5 mg of DCL in terms change from baseline in TSS. Onset of effect based on nasal symptom scores was the same as TSS, but onset of action based on non-nasal symptoms was 3 hours. No statistically significant difference between 5 mg DCL and placebo was seen at any time point for itching ears/palate or tearing of the eyes. The length of time needed to show an onset of effect for nasal congestion, itching of the eyes and rhinorrhea was 1.75 hours, for nasal itching was 4.5 hours and for sneezing was 2 hours. Onset of therapeutic response was 2 hours after drug administration.

Onset of effect after administration of 5 mg of DCL

Parameter	5 mg DCL
Total symptom score	1.75 hours
Total nasal symptom score	1.75 hours
Total non-nasal symptom score	3 hours
Nasal congestion, rhinorrhea, itching eyes	1.75 hours
Nasal itching	4.5 hours
Sneezing	2 hours
Itching ears/palate, tearing eyes	None

Safety: There were no adverse events. There were no clinically significant changes in vital signs.

➤ **Overall Conclusions regarding onset of effect based on the onset of effect studies:** The sponsor has performed three studies that show an onset of effect for 5 mg of DCL of 1.75-2 hours, based on TSS but driven by improvement in nasal symptoms. Two of these studies were crossover studies with a 10 day washout period between treatments. While ten days is an adequate washout period for medication effect, it is less adequate in terms of carryover effect from pollen exposure. The degree to which previous pollen exposure could have influenced treatment in subsequent periods is, therefore, unclear. It is also difficult to explain the consistently later onset of effect in the group that received 7.5 mg as compared with the group that received 5 mg in both EEU studies (see table below).

Onset of effect

Study	parameter	5 mg	7.5 mg
367	TSS	2 hours	3.5 hours
	Total nasal SS	2 hours	2.5 hours
	Total non-nasal	1.75 hours	4.5 hours
448	TSS	1.25 hours	3.5 hours
	Total nasal SS	1.5 hours	3.5 hours
	Total non-nasal	1.75 hours	4 hours
287	TSS	1.75 hours	-----
	Total nasal SS	1.75 hours	-----
	Total non-nasal	3 hours	-----

This reviewer feels that there is inadequate data to support a claim for onset of effect seen after a single 5 mg dose of DCL. The later onset of effect with a larger dose (7.5 mg) raised questions about the validity of the studies as does the washout period in the crossover studies. In addition, the data raises questions about the appropriateness of studies with the Vienna Challenge Unit which has not been validated, especially since onset of effectiveness could not be demonstrated in the only outdoor study. Finally, this reviewer does not believe that a clinically significant change from baseline was demonstrated in any of the studies.

Onset of effectiveness based on 2-4 week repetitive dose studies:

The time required to produce an effect with repetitive administration of DCL at a dose of 5 mg was 2 days in study 223 ($p = 0.02$), longer than 3 days in study 224 ($p = 0.07$ after 4 days), 1 day or less in study 225 ($p = 0.01$) (the second day, i.e. 24 hours after administration of the first dose of DCL, was the first time point at which change from baseline in TSS was measured) and 1 day or less in study 001 ($p = < 0.01$). After repetitive administration of 7.5 mg of DCL, the onset of effectiveness was 1 day or less in 3 studies while no efficacy was demonstrated in study 224.

Time required to demonstrate a statistically significant improvement in mean TSS relative to placebo in studies of 2-4 weeks duration

Study	5 mg DCL	7.5 mg DCL
Study 223	2 days	1 day or less
Study 224	> 3 days	None
Study 225	1 day or less	1 day or less
Study 001	1 day or less	1 day or less

Conclusion: There is adequate data to support a claim for effectiveness of 5 mg of DCL beginning within 2 days of initiating treatment, based on studies 223 and 001.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY STUDIES

Study 357: ECG PD effect with multiple high doses (volume 115)

- ☛ number of patients: 24
- ☛ age range: 20-48 years
- ☛ patient population: healthy volunteers (12 males, 12 females)(QTc less than 420 msec); 10 Caucasian, 14 African-American patients; sequestered during the study (i.e. from at least 48 hours prior to initial drug administration until parameters evaluated on day 11)
- ☛ study design: single center, randomized, double-blind, placebo-controlled, ~~repetitive dose, crossover study~~

- ☛ drug administration: DCL 45 mg (7.5 mg; 6 tablets); fasting on day 10; once daily in the morning
- ☛ periods of study: 10 days of randomized treatment separated by at least a 14 day washout period
- ☛ parameters evaluated:
 - ☛ blood samples for PK over 24 hours; prior to treatment and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration on day 10 and immediately prior to drug administration on days 7, 8, and 9; all plasma samples were evaluated for DCL and 3-OH DCL; Cmax, Cmin, Tmax, AUC and total body clearance
 - ☛ ECGs over 16 hours at baseline and on day 10; hourly for the first 6 hours and then every 2 hours for the next 6 hours and just prior to the first dose at baseline; daily 2 hours after drug administration; 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration on day 10; QTc interval was calculated by the ECG machine using Bazett's formula

- the primary PD parameter was the difference between baseline maximum ventricular rate, PR, QRS, QT and QTc intervals and these same parameters on day 10.
- genotyping by cytochrome-based P450 allelic specific amplification
- vital signs: daily
- laboratory tests: at baseline and at the conclusion of the study
- adverse events

➤ study results:

- pharmacokinetics: the median Tmax for DCL was 5 hours and for 3-OH DCL was 4 hours; Cmax was 57.3 ng/mL and AUC was 944 ng.hr/mL for DCL;
- safety: pharyngitis was seen significantly more frequently in the DCL group than in the placebo group (3 in DCL group, none in placebo group); otherwise, there was no significant difference between the study groups in terms of adverse events; no clinically significant changes were seen in any of the laboratory tests done; no clinically significant changes were noted in vital signs.
- ECG data: There was greater prolongation of the mean QTc interval after administration of DCL than after administration of placebo, but there were no individual patients who had prolongation of the QTc interval above 433 msec and none who had ECG changes consistent with a ventricular arrhythmia. Further assessment of the effect of DCL on the QTc interval can be seen in the table below.

DCL vs placebo in terms of QTc interval and ventricular rate (VR)

Parameter	placebo	DCL	p value
QTc maximum day 10	429 msec	433 msec	-----
QTc maximum change day 1 to day 10	- 18 msec	24 msec	-----
VR maximum day 10	112 bpm	117 bpm	-----
VR maximum change day 1 to day 10	30 bpm	30 bpm	-----
QTc mean diff between max day 1 and day 10	0.3 msec	4.3 msec	P = 0.09
VR mean diff between max day 1 and day 10	4.2 bpm	13.6 bpm	P = 0.00
QTc mean max diff day 1 and day 10; females	0.9 msec	4.7 msec	P = 0.10
VR mean max diff day 1 and day 10; females	0.8 bpm	11.8 bpm	P = 0.02
QTc mean max diff day 1 and day 10; males	- 0.4 msec	3.9 msec	P = 0.31
VR mean max diff day 1 and day 10; males	7.7 bpm	15.4 bpm	P = 0.07
QTc mean diff between max day 1 and day 10	0.1 msec	1.1 msec	P = 0.08
VR mean diff between max day 1 and day 10	5.3 bpm	17.1 bpm	P = 0.00

* **Study 353: (PK and ECG PD of DCL plus erythromycin)(Volume 1.95)**

- **Number of patients: 24 (12 males, 12 females)**
 - **Age range: 19-46 years**
 - **Patient population: healthy volunteers (QTc less than 420 ms)**
 - **Study design: randomized, crossover, third party blind, repetitive dose, placebo-controlled study**
 - **Drug administration: DCL 7.5 mg daily; erythromycin 500 mg q8h; fasting**
-
- **Periods of study: at least 7 day washout between treatments; 10 day treatment with DCL plus Erythromycin and administration of DCL plus placebo for 10 days**
 - **parameters evaluated: ECGs were initially machine-interpreted; subsequently a physician using Bazett's correction interpreted the findings with the option of overruling the machine-interpreted reading; there is no indication of how the physician read the ECGs and whether the physician had expertise in evaluating the QTc interval; vital signs; adverse events; pharmacokinetic data**
 - **Study results: see table below; there was no QTc interval increase greater than 8% compared with baseline; the maximum QTc interval reported after either treatment was 445 msec; maximum prolongation after administration of DCL and erythromycin was 31 msec; the mean difference between the maximum ventricular rate at baseline and after 10 days of treatment was 9.5 bpm after DCL plus placebo and 11.5 bpm after DCL plus erythromycin; chest pain occurred in 3 patients receiving DCL plus erythromycin and no patients who received just DCL; dizziness occurred in 6 patients who received DCL plus erythromycin and one patient who received just DCL.**

pharmacokinetics of DCL with and without erythromycin

Parameter	DCL plus placebo	DCL plus erythromycin
Mean Cmax	6.51 ng/mL	8.07 ng/mL
Mean Tmax	2.88 hours	2.77 hours
Mean AUC	100 ng.hr/mL	114 ng.hr/mL

Pharmacokinetics of 3-OH DCL with and without erythromycin

parameter	DCL plus placebo	DCL plus erythromycin
Mean Cmax	2.98 ng/mL	4.30 ng/mL
Mean Tmax	4.71 hours	4.31 hours
Mean AUC	51.3 ng.hr/mL	72.7 ng.hr/mL

Comparison of ECG parameters with DCL alone and with erythromycin

Parameter	DCL/placebo	DCL/erythromycin	p value
Maximum QT interval day 10	460 msec	439 msec	-----
Maximum change QT interval day 10	-38 msec	-40 msec	-----
Maximum QTc interval day 10	445 msec	445 msec	-----
Maximum change QTc interval day 10	29 msec	31 msec	-----
Maximum ventricular rate day 10	107 bpm	102 bpm	-----
Maximum change ventricular rate day 10	24 bpm	28 bpm	-----
Mean difference maximum QT day 10-1	-8.9 msec	-8.3 msec	0.89
Mean difference maximum QTc day 10-1	7.8 msec	9.8 msec	0.53
Mean difference max vent rate day 10-1	9.5 msec	11.5 bpm	0.31

- no QTc interval increase from baseline greater than 8%
- maximum QTc interval was 445 msec
- maximum QTc prolongation after DCL + erythromycin was 31 msec
- chest pain – 3 patients with DCL + erythromycin; none after DCL
- dizziness – 6 pts after DCL + erythromycin; 1 pt after DCL

Study 352: (DCL plus ketoconazole)(volume 1.89)

- **Number of patients: 24 (12 males; 12 females)(17 African- American)**
 - **Age range: 19-50 years**
 - **Patient population: healthy volunteers**
 - **Study design: single center, randomized, third party blind, placebo-controlled, repetitive dose, crossover study**
 - **Drug administration: DCL 7.5 mg once daily; ketoconazole 200 mg bid**
 - **Periods of study: at least 7 day washout period between 10-day Rx periods**
-
- **Parameters evaluated: ECGs at baseline and after 10 days of treatment; ECGs were obtained 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 28 hours after drug administration at screening and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration on day 10; ECGs were initially machine-read and subsequently read by a physician using Bazett's correction, who could override the machine interpretation; there is no indication of how the ECGs were read and if the physician had expertise in the evaluation of the QTc interval; plasma DCL and Klevels over 24 hours on day 10; k**
 - **Study results: see table below; concomitant administration of DCL and ketoconazole produced a 29-45% increase in the Cmax of DCL, and a 21-39% increase in AUC of DCL; there was an even greater increase in 3-OH DCL with concomitant administration of ketoconazole, 43-77% for Cmax and 72-110% for AUC; there was no increase in QTc interval greater than 5.4%; the maximum QTc after 10 days of treatment with DCL and with DCL plus ketoconazole were 431 and 435, respectively; the mean increase in QTc was 2.3 msec after administration of DCL and 5.4 msec after administration of DCL plus ketoconazole; the maximum prolongation of the QTc interval after administration of DCL and ketoconazole was 22 msec; the mean increase in ventricular rate was 12.2**

Study 354 (volume 1.103) (patients with liver impairment)

- **Number of patients: 20 (8 with normal liver function; 12 with chronic liver disease)(4 female, 16 male)(11 Caucasian, 9 African-American)**
- **Age range: 43-65 years**
- **Patient population: stable chronic liver disease, classified on basis of severity of liver disease; sequestered during the study**
- **Study design: single center, single dose, open, parallel study**
- **Drug administration: 7.5 mg DCL fasting**
- **Periods of study: ~~blood samples over 240 hours after drug~~ administration**
- **Parameters evaluated: adverse events, vital signs, blood samples for PK**
- **Study results: see table below with mean PK parameters; no dose response was established based on the severity of liver disease, but overall, patients with liver disease had 1.7 to 2.4 times greater C_{max} and 1.4 to 2.2 times greater AUC than patients without liver disease; therefore, it is recommended that dosage adjustment be made for patients with liver disease and that this be indicated in the labeling.**

PK for DCL in patients with liver disease

Parameter	Severity of Liver disease			
	mild	moderate	severe	none
C _{max}	5.14 ng/mL	7.04 ng/mL	6.24 ng/mL	2.95 ng/mL
T _{max}	9.63 hours	1.63 hours	2.38 hours	5.5 hours
AUC	406 ng.hr/mL	248 ng.hr/mL	384 ng.hr/mL	181 ng.hr/mL
T _½	77.3 hours	60.6 hours	64 hours	54.3 hours
CL/F	32.2 L/hr	31 L/hr	23.8 L/hr	86.2 L/hr

Study 214: volume 1.86

Number of patients: 20 (17 African-American)

Age range: 19-45 years

Patient population: healthy volunteers

Study design: single center, single dose, randomized, open, crossover study

Drug administration: 5 mg, 7.5 mg, 10 mg, and 20 mg

Periods of study: measurement of PK parameters for 168 hours (7 days) after drug administration

Parameters evaluated: Cmax, Tmax, AUC, t ½, ECGs, vital signs

Study results: see table below;

Parameter	5 mg DCL	7.5 mg DCL	10 mg DCL	20 mg DCL
Mean Cmax	2.18 ng/mL	3.03 ng/mL	3.80 ng/mL	8.08 ng/mL
Mean Tmax	4.55 hours	4.13 hours	4.45 hours	3.90 hours
Mean AUC ng.hr/mL	78	104	126	290
Mean T ½	29.4 hours	31.4 hours	31.7 hours	32.3 hours

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Study 551: effect with and without alcohol on performance measures

Number of patients: 25; 23 patients completed all treatments

Age range: 21-54 years

Patient population: normal volunteers; 14 females and 11 males

Study design: single center, single dose, randomized, placebo-controlled, double-blind, crossover study

Drug administration: 7.5 mg with and without alcohol

Periods of study: ~~4 separate treatment days with a washout of at least 5 days between treatment days~~

Parameters evaluated: 5 psychomotor tests; modified Romberg's test, Stanford Sleepiness scale, Digit Symbol Substitution Test, Serial Add Subtract and Psychomotor Vigilance Test; evaluations were at baseline and 2, 4, 6, 8, and 10 hours after drug administration; the primary efficacy variable was the average score over each treatment day on each psychomotor test.

Study Results: statistical analysis was not performed on the Modified Romberg's Test because most of the observations were the maximum value; In regard to the Stanford Sleepiness Scale, Serial Add Subtract Reaction Time Test, Psychomotor Vigilance Test, and the Digit Symbol Substitution Test, there was a statistically significant difference between the response in patients when they received alcohol and when they did not, for both DCL and placebo, but there was no statistically significant difference between DCL and placebo, when patients received alcohol or did not receive alcohol.

Safety parameters: There were slightly more AEs of specific types noted when patients received both DCL and alcohol compared to when they received placebo and alcohol. For example, fatigue occurred in 25% of

patients when they received DCL and alcohol compared with 17% when they received placebo and alcohol. Similarly, headache occurred in 42% of patients when they received DCL and alcohol compared to 35% when they received placebo and alcohol. The incidence of these AEs was significantly less when patients received either DCL or placebo alone. Two patients had increases of 47% and 44% in pulse rate after receiving DCL and alcohol, compared to one patient who had an increase of 31% after receiving placebo and alcohol. In general, there were no clinically significant changes in vital signs.

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PK studies:

Study 248 (vol 1.81)

Number of patients: 48; 12 patients in each treatment group

Age range: 18-45 years

Patient population: healthy male volunteers

Study design: single center, randomized, double-blind, placebo-controlled, parallel, rising single dose study

Drug administration: ~~SD of 2.5, 5, 10, and 20 mg given at 8 AM~~

Periods of study: evaluation for 168 hours after drug administration

Parameters evaluated: blood samples collected over 168 hours after drug administration for evaluation of PK parameters; ECGs, lab studies, AEs

Study results: see table below; the sponsor states that "a significant treatment effect was observed for the log-transformed AUCs suggesting lack of dose-proportionality in this dose range."

Mean of PK parameters

Parameter	2.5 mg DCL	5 mg DCL	10 mg DCL	20 mg DCL
C _{max} (ng/mL)	0.80	1.67	4.26	8.36
AUC (ng.hr/mL)	9.77	20.70	70.40	158.00
T _{max} ((hr)	3.55	1.70	2.15	2.20
t _{1/2}	Not estimated	Not estimated	Not estimated	24.6

Study 013: (vol 1.83)(rising dose PK study)

Number of patients: 48 (12 patients within each treatment group, 2 of whom received placebo)

Age range: 24-45 years

Patient population: healthy volunteers (males and females)

Study design: single center, randomized, double-blind, placebo-controlled, parallel, rising multiple dose study

Drug administration: 5 mg, 7.5 mg, 10 mg and 20 mg doses of DCL

Periods of study: 14 days of randomized treatment

Parameters evaluated: ECGs, vital signs, laboratory tests, adverse events; blood samples for determination of PK parameters 72 hours following drug administration on day 1; 168 hours after drug was given on day 17

Study results: All adverse events were mild/moderate. The most common adverse event was headache, with no increase in adverse events with increasing dose. There were no clinically significant changes in vital signs or ECGs. Mean values for selected PK parameters after a single dose and repetitive dosing with DCL, can be seen in the table below.

Parameter	5 mg	7.5 mg	10 mg	20 mg
C _{max} (SD)	1.83 ng/mL	2.28 ng/mL	4.08 ng/mL	7.08 ng/mL
C _{max} (RD)	6.33 ng/mL	4.18 ng/mL	7.81 ng/mL	12.3 ng/mL
AUC (SD)	29 ng.hr/mL	27 ng.hr/mL	55 ng.hr/mL	98 ng.hr/mL
AUC (RD)	113 ng.hr/mL	57 ng.hr/mL	135 ng.hr/mL	185 ng.hr/mL
T _{max} (SD)	6 hours	2.95 hours	2.95 hours	3.95 hours
T _{max} (RD)	6.40 hours	4.60 hours	9.50 hours	4.35 hours
T _{1/2} (SD)	33.4 hours	19 hours	34.6 hours	19.2 hours
T _{1/2} (RD)	40.4 hours	18.8 hours	37.4 hours	26.7 hours

There was substantial variability between patients (%CV for Cmax and AUC was 73-107%). A dose response was seen after administration of 10 and 20 mg, but not after administration of 7.5 mg. Dyspepsia was seen in 8 patients at some dose of DCL, compared with no patients in the placebo group. Only one of these patients was thought to have developed this AE because of DCL.

Study 215: (vol 1.101)(food effect)

Number of patients: 18 patients

Age range: 18-45 years

Patient population: ~~healthy volunteers (male and female)~~

Study design: crossover, randomized, open, single dose study

Drug administration: 7.5 mg DCL

Periods of study: at least 7 days between treatments

Parameters evaluated: evaluation including blood samples for 168 hours after drug administration

Study results: see table below; food did not appear to have any appreciable effect on oral bioavailability.

Parameter	fed	fasting
Cmax	3.53 ng/mL	3.30 ng/mL
AUC	73.8 ng.hr/mL	77.7 ng.hr/mL
Tmax	4.75 hrs	3.36 hrs
T _{1/2}	20.9 hrs	22.0 hrs

Study 97: (vol 1.71)

Number of patients: 6 patients

Age range: 18-40 years

Patient population: healthy male volunteers

Study design: single dose, open study

Drug administration: 10 mg of C14 labeled DCL

Periods of study: patients stayed in CRU for 12 hours prior to drug administration and 240 hours after drug administration

Parameters evaluated: PK parameters, adverse events

Study results: see table below; radioactivity was excreted in the urine (41%) and feces (47%); extensively metabolized through hydroxylation and subsequent glucuronidation.

Parameter	10 mg DCL
C_{max}	4.32 ng/mL
T_{max}	5.80 hours
T_½	19.5 hours
AUC	77.7 ng.hr/mL

Study 311; (volume 109)

Number of patients: 63 enrolled (61 Caucasian), 53 completed all 3 treatment periods

Age range: 19-41 years

Patient population: healthy male volunteers, sequestered

Study design: crossover, randomized, open, single dose study

Drug administration: 5 mg DCL, 5 mg capsules of DCL polymorphs (2 formulations); all administered fasting

Periods of study: ~~three way crossover~~

Parameters evaluated: vital signs, ECGs, plasma PK for DCL for 120 hours after drug administration

Study results: see table below, demonstrating bioequivalence of the 3 formulations.

Mean PK parameters

Parameter	formulation1 capsule	formulation 2 capsule	5 mg tablet
Cmax (ng/mL)	1.9	1.9	2.1
Tmax (hours)	3.1	3.3	2.7
AUC (ng.hr/mL)	34	37	36
T ½ (hours)	23	22	22

Study 356: (volume 106)

Number of patients: 48 (12 Caucasian males, 12 African-American males, 12 Caucasian females, 12 African-American females)

Age range: 19-45 years

Patient population: healthy volunteers; sequestered

Study design: single center, repetitive dose, open, parallel study

Drug administration: 7.5 mg DCL on days 4-17

Periods of study: 14 days of treatment

Parameters evaluated: ECGs, vital signs, adverse events, ~~plasma DCL~~

Study results: see table below; mean Cmax and AUC for DCL were higher in African-American patients than in Caucasian patients after single and multiple doses of DCL; on the other hand, mean Cmax and AUC for 3-OH DCL were generally slightly higher in Caucasian patients; the differences are not great enough to warrant any dosage adjustment in African-American patients.

Mean values of DCL after single dose

Parameter	white males	white females	black males	black females
Cmax (ng/mL)	3.46	3.57	3.00	4.05
Tmax (hours)	3.04	2.54	5.58	3.42
AUC (ng.hr/mL)	41.2	42.2	44.6	53.3
T ½ (hours)	28	21	31	23

Mean values for 3-OH DCL after single dose

Parameter	white males	white females	black males	black females
Cmax (ng/mL)	1.45	1.66	1.07	1.62
Tmax (hours)	3.46	4.50	5.92	5.00
AUC (ng.hr/mL)	18.5	23.8	15.4	23.0
T ½ (hours)	33	25	52	31

Mean values of DCL after multiple doses

Parameter	white males	white females	black males	black females
Cmax (ng/mL)	6.05	5.46	7.52	6.73
Tmax (hours)	2.29	2.50	5.08	3.33
AUC (ng.hr/mL)	98.1	74.5	135	107
T ½ (hours)	36	30	42	35

Mean values of 3-OH DCL after multiple doses

Parameter	white males	white females	black males	black females
Cmax (ng/mL)	2.31	2.85	2.09	2.98
Tmax (hours)	5.04	4.67	4.17	3.75
AUC (ng.hr/mL)	38.1	48.1	32.7	50.6
T ½ (hours)	48	37	52	46

Study 117:

(comparison of systemic availability of DCL and loratadine)(vol 73)

Number of patients: 24 (18 males, and 6 females)(20 Caucasian, 4 African-American)

Age range: 19-41 years

Patient population: healthy volunteers; sequestered

Study design: single center, randomized, open, repetitive dose, crossover study

Drug administration: 5 mg per day and 7.5 mg per day of DCL and 10 mg per day of loratadine

Periods studied: 10 days of treatment with 3 treatment regimens each separated by at least 14 days

Parameters evaluated: plasma samples for up to 96 hours after drug administration; urine samples for 24 hours after drug administration; adverse events, vital signs

Study results: see table below; steady state was reached by day 10 after administration of each treatment; this study was of particular importance because the sponsor had been told that long-term safety studies of 6-12 months duration would not be necessary if the systemic exposure after administration of 5 mg of DCL was less than the systemic exposure after administration of 10 mg of loratadine.

Mean PK values for DCL and loratadine at steady state

Parameter	5 mg DCL	7.5 mg DCL	10 mg loratadine
C _{max} (ng/mL)	4.89	7.30	6.03
T _{max} (hours)	3.08	3.23	2.17
AUC (ng.hr/mL)	72	104	75
T _{1/2} (hours)	35	34	33
Relative bioavailability	C _{max} - 79 AUC - 95	C _{max} - 117 AUC - 141	-----

Mean PK values for 3-OH DCL and loratadine at steady state

Parameter	5 mg DCL	7.5 mg DCL	10 mg loratadine
C _{max} (ng/mL)	1.62	2.30	1.73
T _{max} (hours)	5.06	4.38	3.29
AUC ng.hr/mL)	23.1	34.3	23.4
T _{1/2} (hours)	49	47	45
Relative bioavailability	C _{max} - 97 AUC - 100	C _{max} - 142 AUC - 147	-----

Mean PK values for 3-OH DCL glucuronide and loratadine at steady state

Parameter	5 mg DCL	7.5 mg DCL	10 mg loratadine
C_{max} (ng/mL)	29.4	46.0	29.9
T_{max} (hours)	8.04	7.38	7.48
AUC (ng.hr/mL)	488	735	489
T_{1/2} (hours)	35	37	28
Relative bioavailability	C_{max} - 103 AUC - 102	C_{max} - 163 AUC - 153	-----

Relative bioavailability = percent of DCL to 10 mg loratadine

Study 275: multiple dose PK study (volume 78)

Number of patients: 113 (57 males, 56 females)(95 Caucasian, 18 African-American)

Age range: 19-70 years

Patient population: healthy volunteers

Study design: open, repetitive dose study

Drug administration: 5 mg once daily for 10 days

Periods of study: 10 days of treatment

Parameters evaluated: blood samples for PK parameters for 120 hours after drug administration on day 10

Study results: see table below.

Mean PK parameters for DCL in different age groups

Parameters	19-45 years	46-64 years	65-70 years
C _{max} (pg/mL)	3.83	3.92	4.69
T _{max} (hours)	3.35	2.98	2.76
AUC (pg.hr/mL)	55.4	54.1	67.8
T _{1/2} (hours)	25.3	26.1	33.7
CL/F (kg-mL/hr)	20.4	16.8	19.7

Mean PK parameters for 3-OH DCL in different age groups

Parameters	19-45 years	46-64 years	65-70 years
C _{max} (pg/mL)	1.92	2.12	2.05
T _{max} (hours)	4.80	4.90	4.35
AUC (pg.hr/mL)	30.7	34.3	34.6
T _{1/2} (hours)	34.7	35.6	41.8

Study 248: Volume 81

Number of patients: 48; 12 in each of 4 group; 10 in each group received DCL and 2 received placebo

Age range: adults

Patient population: healthy volunteers

Study design: single center, randomized, double-blind, placebo-controlled, parallel, rising single dose study

Drug administration: 2.5, 5, 10, and 20 mg

Periods of study: evaluation for 168 hours after drug administration

Parameters evaluated: ECGs, vital signs, adverse events, blood samples for PK parameters

Study results:

Parameter	2.5 mg DCL	5 mg DCL	10 mg DCL	20 mg DCL
C _{max} (ng/mL)	0.80	1.67	4.26	8.36
AUC (ng.hr/mL)	9.77	20.70	70.40	158.00
T _{max} (hours)	3.55	1.70	2.15	2.20
T _{1/2} (hours)	-----	-----	-----	24.6

Study 355: (volume 10.9)(patients with renal impairment)

- **number of patients:** 37 patients; 12 in group 1 (creatinine clearance > 80 mL/min); 7 in group 2 (creatinine clearance 51-80 mL/min); 6 in group 3 (creatinine clearance 30-50 mL/min); 6 in group 4 (creatinine clearance < 30 mL/min); and 6 in group 5 (hemodialysis-dependent)

- **age range:** 26-70 years

- **patient population:** patients with normal renal function as well as patients with stable chronic renal insufficiency and severe chronic renal insufficiency undergoing hemodialysis; 25 Caucasian; 9 African-American, 1 Asian-American and 2 Hispanic; 26 males, 11 females

- **study design:** single center, single dose, parallel, open-label study

- **drug administration:** DCL 7.5 mg

- **periods of study:** at screening, sequestered for 36 hours to determine creatinine clearance; admitted for drug administration and followed subsequently for 96 hours if in groups 1-4 (sequestered for 48 hours) and for 72 hours if in group 5 following the hemodialysis and nonhemodialysis periods(sequestered for 48 hours)

➤ parameters evaluated: Cmax, Tmax, AUC: adverse events, vital signs, labs

➤ study results:

Mean PK values in patients with and without renal insufficiency

parameter	group 1	group 2	group 3	group 4	group 5
Cmax (ng/mL)	3.65	4.56	5.39	6.20	5.79
Tmax (hours)	2.63	4.64	4.00	2.42	2.58
AUC (ng.hr/mL)	62.4	160	132	143	116
T ½ (hours)	19.3	37.0	45.8	30.1	-----
CL/F (mL/min)	2115	1081	1068	882	1037

Comment: Similar to the study in patients with liver impairment, there did not appear to be a direct correlation between the severity of renal disease and systemic availability of DCL. Nevertheless, there was substantially more systemic availability of DCL (up to 2.5 times in terms of AUC) in patients with some degree of renal insufficiency. Therefore, the labeling should be changed to indicate that lower doses of DCL may be indicated in patients with renal impairment.

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ON ORIGINAL

Integrated Summary of Safety

3282 patients; 2346 patients received DCL; 1044 received placebo; there were 2499 patients in placebo-controlled multiple dose studies (1838 received DCL and 661 received placebo)(NOTE: the sponsor was told that long term safety data [6-12 months] was not needed provided the systemic exposure from 5 mg of DCL was less than seen with 10 mg loratadine.)

Adverse Events:

AEs (number (%) in multiple dose studies
DCL dose

AEs	2.5 mg	5 mg	7.5 mg	10 mg	20 mg	placebo
Number pts	173	659	662	172	172	172
All AEs	75 (43)	325 (49)	301 (45)	76 (44)	81 (47)	298 (45)
Related AEs	34 (20)	111 (17)	102 (15)	32 (19)	38 (22)	83 (13)
Severe AEs	18 (10)	75 (11)	72 (11)	12 (7)	12 (7)	64 (10)
Severe and related AEs	8 (5)	22 (3)	24 (4)	6 (3)	7 (4)	18 (3)

Only dry mouth (4% in 5 mg DCL group, 2% in placebo group) and pharyngitis (5% in 5 mg DCL group, 2% in placebo group) occurred with a 2% or greater incidence in the 5 mg DCL group than in the placebo group in the multiple dose studies. Of treatment-related AEs, only headache (6% in the DCL 5 mg group, 4% in the placebo group) occurred with a 2% or greater incidence in the 5 mg DCL than in the placebo group in the multiple dose studies. There were no severe AEs that occurred with a significantly greater frequency in the 5 mg DCL group than in the placebo group in the multiple dose studies. There was no significant difference between the incidence of AEs requiring discontinuation from the study in the 5 mg DCL group and the placebo group. There were 3 patients who discontinued the study because of arrhythmia, palpitation or tachycardia, one in the 10 mg DCL, one in the 20 mg DCL and one in the placebo group and one patient who discontinued treatment because of mild chest pain after receiving 7.5 mg of DCL. The ECGs on all these patients were normal. The incidence of AEs was slightly higher in females

than in males due to a greater incidence of headache. The overall incidence of headache was no greater in women who received DCL 5 mg than in women who received placebo, although the incidence of treatment related headache was 7% in women who were received 5 mg DCL and 4% of women who received placebo. There was no significant difference in AEs based on age or race. A comparison of major adverse effects produced by antihistamines, i.e. dry mouth, fatigue and somnolence, in patients who received desloratadine and patients who received placebo, can be seen below.

**Incidence of sedation and other possible antihistaminic effects:
comparison of 5 mg of DCL and placebo:**

Study 001:

**Dry mouth – 3% DCL, 2% placebo
Fatigue – 3% DCL, < 1% placebo
Somnolence – 3% DCL, 2% placebo**

Study 225:

**Dry mouth – 4% DCL, 3% placebo
Fatigue – 5% DCL, 4% placebo
Somnolence – 3% DCL, 4% placebo**

Study 224:

**Dry mouth: 5% DCL, 1% placebo
Fatigue: 2% DCL, 1% placebo
Somnolence: 2% DCL, 2% placebo**

Study 223:

**Dry mouth: 3% DCL, 2% placebo
Fatigue: 3% DCL, 1% placebo
Somnolence: 3% DCL, 2% placebo**

Integrated summary of safety:

Dry mouth: 4% DCL, 2% placebo

Fatigue: 4% DCL, 2% placebo

Somnolence: 3% DCL, 2% placebo

- **laboratory tests:** There was no significantly greater median percent change from baseline for hematologic or blood chemistry parameters after administration of 5 mg of DCL than there was after administration of placebo in the multiple dose studies. In these studies, there was not a significantly greater number of patients in the group that received DCL 5 mg than in the group that received placebo who had a potentially clinically significant change from baseline to endpoint for any laboratory parameter, e.g the number and percentage of patients who had an increase above the normal reference range for liver function tests was comparable in the 5 mg DCL and placebo groups. There was one patient in the 5 mg DCL group that had an increase in SGOT from 17 U/L at screening to 227 U/L (NRR = 0-41 U/L). There were a few patients in the multiple dose studies who received higher doses of DCL who also had an increase in SGOT or SGPT to a level above the upper limit of the normal reference range, while no such changes were seen in the placebo group.
- **vital signs:** There were no significant changes in mean values or percent change from baseline in regard to any vital sign in the group of patients that received DCL in the multiple dose studies and what changes occurred were consistent with the changes seen in the placebo group. The number and percent of patients in the 5 mg DCL and the placebo groups in the multiple dose studies who had 10% or greater change from baseline in diastolic blood pressure, systolic blood pressure and heart rate were comparable.
- **ECGs:** ECGs were done at screening and endpoint, 1-3 hours after administration of the last dose of study medication, in the multiple dose studies. All QTc intervals were recalculated by the sponsor using the Fridericia formula. One patient in the multiple dose studies who

received 5 mg DCL had a 7% increase in QTc interval from 431 msec at screening to 465 msec at endpoint, that was not associated with symptoms. The mean QTc interval in the multiple dose studies decreased from 1-4% in the DCL treatment groups and increased 1% in the placebo group. There was a dose-related increase in ventricular rate seen in patients who received DCL in the multiple dose studies from 3.1% in the group that received 2.5 mg DCL to 7.4% in the group that received 20 mg DCL. The increase in ventricular rate in the group that received placebo, on the other hand, was 1.1%. There was no significant difference in the number or percent of patients who had an increase in ventricular rate, QT interval or QTc interval of 10% or more between the group that received 5 mg DCL and the group that received placebo in the multiple dose studies. Three patients, one each in the 7.5 mg, 10 mg and 20 mg DCL groups, discontinued because of adverse events of possible cardiovascular origin, that included tachycardia in 2 patients, one with a previous history and one on thyroid medication, and mild chest pain. There was no significant difference between DCL and placebo in terms of any of the cardiovascular parameters evaluated when analyzed in terms of age, gender or race.

- **hepatic effect:** There was no significant difference in the number or percentage of patients that received 5 mg of DCL or placebo in terms of increases from normal to levels above the upper limits of normal as defined in the study for alkaline phosphatase, SGOT, SGPT, LDH, or total bilirubin. In one study (study 354), evaluating PK parameters in patients with and without chronic liver disease, a greater systemic bioavailability was seen in the group that had liver disease.

APPEARS THIS WAY
ON ORIGINAL

Amendment of 20 March 2000 with correction of QTc values

➤ **background:** The sponsor corrected the QT interval for heart rate using the Fridericia formula (all ECGs were machine-read). At our request, the sponsor has now submitted corrected QT intervals using the Bazett formula (all ECGs were machine read). ECGs were done at screening and within 1-3 hours after the last dose.

➤ **pooled data** from the 4 multiple dose studies in patients with SAR: At a dose of 7.5 mg and higher, there was dose-response in terms of ventricular rate, with the mean increase being 1.4 bpm after 7.5 mg of DCL. 2.3 bpm after 10 mg of DCL and 4.5 bpm after 20 mg of DCL. Substantially larger numbers of patients received a dose of 7.5 mg of DCL (655) than received 10 mg or 20 mg (169). Nevertheless, this data suggests that ~~DCL has an anticholinergic effect at higher doses.~~ Using the Bazett's correction, more prolongation of the mean QT interval in the pooled data from the multiple dose SAR studies was seen at all doses than was seen using the Fredericia correction (see table below). There was not a consistent or clinically significant increased incidence of increased QT of 10->20% compared to placebo at any dose of DCL and no dose-response was seen in regard to this parameter. There was an increase in the QTc interval using Bazetts correction in females who received 7.5 mg DCL, while there was a decrease in males who received the same dose.

**Mean change (% change) from baseline
Pooled Data from all Multiple Dose SAR Studies**

Parameter	Dose of DCL					
	2.5 mg	5 mg	7.5 mg	10 mg	20 mg	placebo
Mean HR after Rx	1.5 bpm (3.1%)	0.8 bpm (2.1%)	1.4 bpm (2.9%)	2.3 bpm (4.4%)	4.5 bpm (7.4%)	0.1 bpm (1.1%)
QT interval (msec)	-1.7 msec (-0.3%)	-3.2 msec (-0.6%)	-2.4 msec (-0.5%)	-2.6 msec (-0.4%)	-9.3 msec (-0.2%)	-0.4 msec (0.6%)
QTc (Fredericia)	0.7 msec (0.3%)	-1.5 msec (-0.3%)	0.1 msec (0.1%)	1.5 msec (0.5%)	-1.4 msec (-0.2%)	-0.2 msec (0.7%)
QTc (Bazetts)	2.0 msec (0.7%)	-0.6 msec (none)	1.5 msec (0.5%)	3.8 msec (1.1%)	2.8 msec (1.1%)	-0.1 msec (0.8%)

Number of patients (% of patients) with 10% or greater change from baseline in QTc interval using Bazetts correction

treatment	10-14%	15-19%	20% or greater
2.5 mg DCL	9 (5%)	None	1 (1%)
5 mg DCL	11 (2%)	1 (<1%)	1 (<1%)
7.5 mg DCL	12 (2%)	4 (1%)	3 (<1%)
10 mg DCL	7 (4%)	1 (1%)	1 (1%)
20 mg DCL	7 (4%)	2 (1%)	None
Placebo	11 (2%)	3 (<1%)	3 (<1%)

Number of patients (% of patients) with > 10 msec increase in QTc interval using Bazetts correction

Change from Baseline	N = 172 2.5 mg	N = 651 5 mg	N = 655 7.5 mg	N = 169 10 mg	N = 169 20 mg	N = 645 placebo
11-20 msec	24 (14%)	104 (16%)	98 (15%)	24 (14%)	27 (16%)	93 (15%)
21-30 msec	14 (8%)	42 (6%)	55 (8%)	21 (12%)	15 (9%)	55 (8%)
31-40 msec	8 (5%)	17 (3%)	21 (3%)	6 (4%)	3 (2%)	17 (3%)
41-50 msec	3 (2%)	6 (1%)	7 (1%)	5 (4%)	4 (3%)	8 (1%)
51-60 msec	4 (2%)	4 (0.6%)	3 (0.5%)	2 (1%)	2 (1%)	3 (0.5%)
61-70 msec	0	1 (0.2%)	2 (0.5%)	1 (1%)	1 (1%)	1 (0.2%)
71-80 msec	1 (0.6%)	0	4 (0.6%)	0	0	0
81-90 msec	0	1 (0.2%)	0	0	0	2 (0.3%)
91-100 msec	0	0	0	1 (1%)	0	0
> 100 msec	0	0	0	0	0	1 (0.2%)

study 001: The same effect seen in the pooled data (see table above) was seen in this study (see table below). Using the Fredericia formula, there were 2 patients in the 2.5 mg, 7.5 mg and 10 mg DCL groups who had a 15-19% increase the QTc interval compared to none in the placebo group. Using the Bazetts formula, there were 9, 5, 7 and 7 patients in the 2.5 mg, 5 mg, 10 mg and 20 mg DCL groups, respectively, who had a 10-14% increase in the QTC interval, compared to 3 in the placebo group.

**Mean change (% change) from baseline
Data from Study 001**

Parameter	2.5 mg	5 mg	7.5 mg	10 mg	20 mg	placebo
Mean HR after Rx	1.5 bpm (3.1%)	2.2 bpm (4.4%)	2.6 bpm (5%)	2.3 bpm (4.4%)	4.5 bpm (7.4%)	None (0.9%)
QT interval (msec)	-1.7msec (-0.3%)	-6.1 msec (-1.3%)	-2.8 msec (-0.6%)	-2.6 msec (-0.4%)	-9.3 msec (-2.2%)	3.7 msec (3.0%)
QTc (Fredericia)	0.7 msec (0.3%)	-1.1 msec (-0.2%)	2.4 msec (0.7%)	1.5 msec (0.5%)	-1.4 msec (2.8%)	3.5 msec (3.2%)
QTc (Bazetts)	3.0 msec (0.7%)	1.4 msec (0.5%)	5.1 msec (1.4%)	3.8 msec (1.1%)	2.8 msec (0.9%)	3.4 msec (3.5%)

➤ **study 223:** There was no significant difference in regard to QTc interval when measured using the Fredericia and the Bazetts formula (see table below).

**Mean change (% change) from baseline
Data from Study 223**

Parameter	5 mg	7.5 mg	placebo
Mean HR after Rx	0.9 bpm (2.4%)	- 0.3 bpm (0.4%)	1.5 bpm (3.1%)
QT interval (msec)	-5.5 msec (-1.2%)	1.9 msec (0.6%)	-4.7 msec (-1.0%)
QTc (Fredericia)	-3.4 msec (-0.8%)	1.4 msec (0.4%)	-1.8 msec (-0.3%)
QTc (Bazetts)	-2.4 bpm (-0.5%)	1.2 msec (0.4%)	-0.2 msec (0.1%)

➤ **study 224:** The mean difference in QTc interval change from baseline using the Fredericia and the Bazetts formulas can be seen

in the table below. There was a slightly greater number of patients in the 5 mg DCL group that had a 10-14% increase and a 15-19% increase in QT interval (7,1) than in the 7.5 mg group (3,0) or the placebo group (5,0). But there was one patient in the placebo group who had > 20% increase in QT compared to none in the

DCL groups. There was no greater incidence of any degree of prolongation of the QT corrected by either the Fredericia or the Bazetts formula in either DCL group than in the placebo group.

Mean change (% change) from baseline
Data from Study 224

Parameter	5 mg	7.5 mg	placebo
Mean HR after Rx	0.3 bpm (1.1%)	1.4 bpm (2.8%)	-0.1 bpm (0.7%)
QT interval (msec)	-0.1 msec (0.2%)	-4.9 msec (-1.1%)	-1.7 msec (-0.2%)
QTc (Fredericia)	0.4 msec (0.2%)	-2.6 msec (-0.5%)	-1.6 msec (-0.3%)
QTc (Bazetts)	0.7 msec (0.3%)	-1.3 msec (-0.2%)	-1.6 msec (-0.3%)

➤ ~~Study 225: The difference in QTc interval change from baseline using the Fredericia and the Bazetts formulas can be seen in the table below.~~ There was a greater incidence of QT prolongation of 10-14% in the 5 mg DCL (10 patients) and the 7.5 mg DCL (7 patients) groups than in the placebo group (5 patients). There was a slightly greater incidence of QT prolongation of 10-14% using the Bazetts formula for correction but not the Fredericia formula.

Mean Change (% change) from baseline
Data from Study 225

Parameter	5 mg	7.5 mg	placebo
Mean HR after Rx	-0.3 bpm (0.2%)	1.6 bpm (3.4%)	-0.8 bpm (-0.4%)
QT interval (msec)	-1.1 bpm (none)	-3.8 bpm (-0.8%)	0.8 bpm (0.4%)
QTc (Fredericia)	-1.8 bpm (-0.3%)	-0.8 bpm (-0.2%)	-1.2 bpm (-0.2%)
QTc (Bazetts)	-2.1 bpm (-0.4%)	0.7 bpm (0.3%)	-2.3 bpm (-0.4%)

➤ Based on individual patient data using Bazetts correction, and a strict cut-off of 460 msec as a potentially abnormal prolongation of the QTc interval, the number and percentage of patients having some degree of abnormal prolongation of the QTc interval can be seen in the table below.

Number (percentage) of patients with QTc interval \geq 460 msec from pooled data

QTc	baseline	placebo	2.5 mg	5 mg	7.5 mg	10 mg	20 mg
\geq 460 msec	29 (1%) N = 2461	11 (2%) N = 645	1 (0.6%) N = 172	10 (2%) N = 651	6 (1%) N = 655	None N = 169	6 (4%) N = 169
\geq 470 msec	23 (1%)	2 (0.3%)	None	None	3 (0.4%)	None	None
\geq 480 msec	8 (0.4%)	None	None	None	1 (0.1%)#	None	None
\geq 490 msec	8 (0.4%) *	None	None	None	1 (0.1%) #	1 (0.5%)#	None

* There were 8 patients who had a QTc interval of 490 msec or more at baseline (529, 503, 517, 500, 499, 491, 497, and 493). There were two patients who had a QTc interval of 490 or more after taking DCL, one whose QTc interval went from 410 at baseline to 490 msec after receiving 7.5 mg (a change of 80 msec)(heart rate = 67) and one whose QTc interval went from 453 at baseline to 498 msec after receiving 10 mg of DCL (a change of 45 msec)(heart rate = 95).. In addition, there was one patient whose QTc went from 448 msec to 483 msec (a change of 35 msec).

CONCLUSION: No clinically significant effect of DCL on the QTc interval using Bazetts correction was seen based on: 1) mean change in QTc interval from baseline to the end of treatment; 2) number of patients with a 10% or greater change in QTc interval from baseline after treatment; or 3) percentage of patients with a QTc interval of 460 msec or greater after treatment with DCL.

APPEARS THIS WAY
ON ORIGINAL

➤ Review Methods

➤ Conduction of Review: Assessment of this NDA was initiated with a review of the sponsor's overall clinical program for this drug, including studies with other formulations and directed studies not included in the NDA (e.g. fexofenadine non-responder study). Minutes of meetings and telecons with the sponsor were reviewed, as well as notes from previous reviewers. Input was obtained from other disciplines, especially statistics and biopharmaceutics. The four key studies supporting the sponsor's claim for safety and effectiveness, beginning with the only 4 week study, were the first part of the NDA reviewed producing a conclusion on the approvability of desloratadine. The four onset of effectiveness studies were then reviewed, in regard to labeling and potential marketing claims. ~~The clinical pharmacology studies were~~ reviewed next, particularly the high dose study and the interaction studies with erythromycin and ketoconazole, which formed the basis for a determination of the cardiac safety of desloratadine. In this regard, the sponsor was asked to provide us with further data on a few patients who developed chest pain or dizziness and on the methods used for calculating QTc intervals. The labeling was reviewed in regard to dosing recommendations in patients with renal or hepatic insufficiency.

➤ Materials reviewed: Volumes 71, 73, 78, 81, 83, 86, 89, 95, 101, 103, 106, 109, 115, 119 and 120-141 of the NDA were reviewed. The IND was reviewed in regard to specific issues that arose in the review of the NDA. Submission of data by the sponsor clarifying aspects of the NDA were also reviewed.

➤ Data quality and integrity:

➤ DSI Auditing of Studies: -----

It was found that _____ had not adhered to all pertinent federal regulations and/or good clinical investigational practices in study _____ by failing to report _____

who was a clinical investigator in studies 001 and 224 and was found to have conducted study 224 in compliance with federal regulations (NAI classification). who was a clinical investigator in study 225 was found to have conducted the study in compliance with federal regulations (NAI classification). was a clinical investigator in studies 001, 223, and 225. He was found to have conducted study 225 in compliance with federal regulations (NAI classification).

▼ **Use in special populations:** Significantly more systemic availability of desloratadine occurs in patients with renal or hepatic impairment, requiring some dose adjustment in these populations. Systemic availability was slightly greater in woman than in men, but not to a degree necessitating any dose adjustment. There was variability in the pharmacokinetics of DCL in Caucasian and African-American patients, that will require further evaluation by the sponsor (see Biopharm review). There was no significant difference in response based on age, although only small numbers of elderly patients were studied.

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ON ORIGINAL

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the approval package consisted of draft labeling

MEDICAL OFFICER REVIEW

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

APPLICATION #: NDA 21,165

APPLICATION TYPE: NDA supplement

SPONSOR: Schering

PRODUCT/PROPRIETARY NAME: Clarinex

USAN Established Name: Desloratadine

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral tablets

MEDICAL REVIEWER: Nicklas

REVIEW DATE: 12 December 2001

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
5 and 7 December 2001	5 and 7 December 2001	Safety update and labeling	see overview below

Overview of Application/Review: This submission contains a safety update as requested by the Division covering the period from 16 January 2001 to 1 December 2001. This includes post-marketing drug surveillance data from other countries and data from two recently completed clinical studies in this country. A total of 529 adverse events in 293 patients are reported. The most commonly spontaneously reported adverse events were therapeutic response decrease (7.2%), headache (6%), dizziness (4.2%), somnolence (3.8%), fatigue (3.6%), nausea (2.8%), tachycardia (2.5%) and dyspnea (2.1%).

Given the data in the spontaneous reporting system, a sentence should be added to the Adverse Reactions section of the labeling, which reads: "The following spontaneous adverse events have been reported during the marketing of desloratadine: tachycardia, and rarely hypersensitivity reactions (such as rash, pruritis, edema, dyspnea, and anaphylaxis) as well as elevated liver enzymes, including bilirubin." There were no significant types of adverse events that were consistently considered to be related to administration of desloratadine. With the minor change proposed above (or similar wording) for the labeling, this drug product remains approvable.

Outstanding Issues:

Recommended Regulatory Action:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDA's:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ 12/18/01 Date: _____
Medical Team Leader: /S/ 12/19/01 Date: _____

MEDICAL OFFICER REVIEW

OCT 24 2000

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: NDA 21,165

APPLICATION TYPE: Original amendment

SPONSOR: Schering

PRODUCT/PROPRIETARY NAME: Clarinex

USAN Established Name: Desloratadine

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral (tablet)

MEDICAL REVIEWER: Nicklas

REVIEW DATE: 29 September 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
17 February 2000	18 February 2000	4 month safety update	see overview below

Overview of Application/Review: This 4 month safety update included data on 169 additional patients, 165 of whom received 5 or 7.5 mg of desloratadine for 1-7 days. Included were data from 42 patients who received 10 mg of cetirizine, 43 who received 50 mg of diphenhydramine and 94 who received placebo. Interim data was included from study POO272 evaluating the effect of desloratadine in patients with liver disease. There were 3 out of 9 patients with hepatic impairment who had adverse reactions compared to 5 out of 9 healthy volunteers. Another study evaluated the effect of desloratadine in patients with renal impairment (study C98-355). In the interim data from this study, 2 out of 6 patients in each of the moderate, severe and end-stage renal disease groups had an adverse event, while there were no adverse events in normal volunteers. One patient in the severe chronic renal insufficiency group had mildly elevated liver function tests, which returned to normal with follow-up and were considered possibly related to treatment. No clinically significant laboratory values or vital signs were noted after administration of desloratadine. There was no data in this 4 month safety update that changes the recommendation that this drug is approvable.

Outstanding Issues: none

Recommended Regulatory Action: approval

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed _____

NDA's:

Efficacy / Label Supp.: x Approvable _____ Not Approvable _____

Signed: Medical Reviewer: _____

Date: 10/29/2000

Medical Team Leader: _____

Date: 10/24/00

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: NDA 21,165

APPLICATION TYPE: Labeling supplement

SPONSOR: Schering

PRODUCT/PROPRIETARY NAME: Clarinex

USAN Established Name: Desloratadine

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral (tablets)

Nicklas

REVIEW DATE: 16 October 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
4 October 2000	4 October 2000	Labeling supplement	see overview below

Overview of Application/Review: There are a number of changes required in the labeling submitted by the sponsor. Changes, as indicated in the review below, are required in the Mechanism of Action, Special Populations, Renally Impaired, Hepatically Impaired, Drug Interactions, Effects on QTc, Clinical Trials, Precautions, Geriatric Use, Overdosage, and Dosage and Administration sections. There are discussed in detail below.

Outstanding Issues: changes in the labeling

~~Recommended Regulatory Action: the proposed changes in the labeling should be conveyed to the sponsor~~

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDA's: _____

Efficacy / Label Supp.: Approvable _____ Not Approvable

Signed: Medical Reviewer: [Signature] HD Date: 10/17/2000

Medical Team Leader: [Signature] Date: 10/17/00

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the approval package consisted of draft labeling